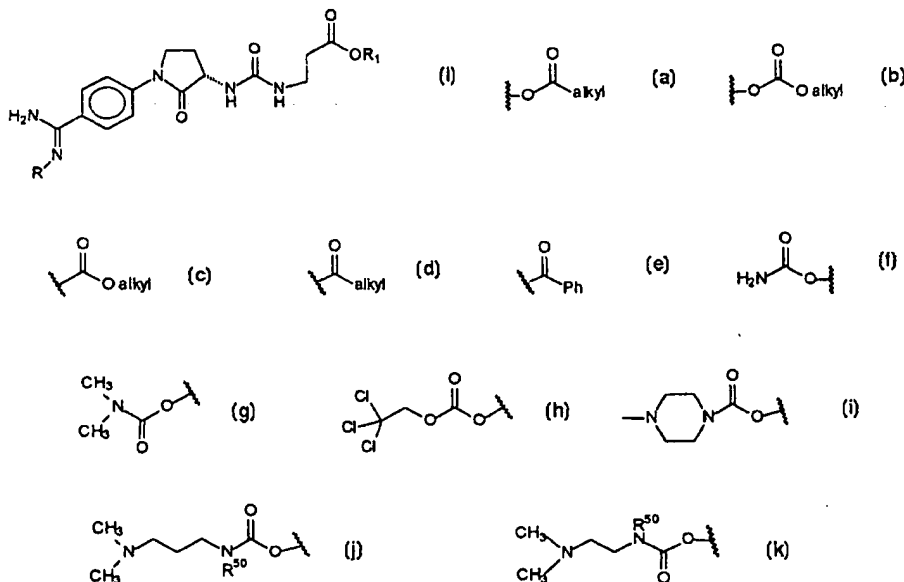




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(54) Title: DOUBLE PRODRUGS OF POTENT GPIIb/IIIa ANTAGONISTS



## (57) Abstract

The present invention relates to double prodrugs of pharmacologically active glycoprotein IIb/IIIa antagonists of formula (I), wherein  $R_1$  is selected from the group consisting of lower alkyl of about 2 to about 8 carbon atoms, cycloalkyl, and aralkyl; R is selected from the group consisting of alkoxy, formula (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), wherein  $R^{50}$  is H or alkyl; and formula (k), wherein  $R^{50}$  is H or alkyl; and pharmaceutically acceptable salts thereof.

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## DOUBLE PRODRUGS OF POTENT GPIIb/IIIa ANTAGONISTS

The present application claims priority under 35 USC §119(e) of United States Provisional Patent Application Serial No. 60/088,996 filed June 11, 1998.

### Field of the Invention

The present invention relates to double prodrugs of pharmacologically active glycoprotein IIb/IIIa antagonists.

### Background of the Invention

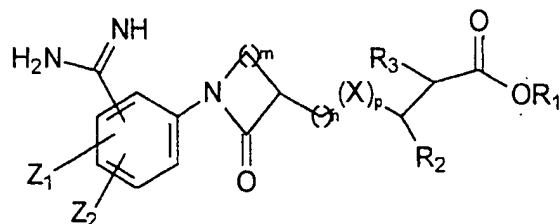
Fibrinogen is a glycoprotein present as a normal component of blood plasma. It participates in platelet aggregation and fibrin formulation in the blood clotting mechanism.

Platelets are cellular elements found in whole blood which also participate in blood coagulation. Fibrinogen binding to platelets is important to normal platelet function in the blood coagulation mechanism. When a blood vessel receives an injury, the platelets binding to fibrinogen will initiate aggregation and form a thrombus. Interaction of fibrinogen with platelets occurs through a membrane glycoprotein complex, known as GP IIb/IIIa; this is an important feature of the platelet function. Inhibitors of this interaction are useful in modulating platelet thrombus formation.

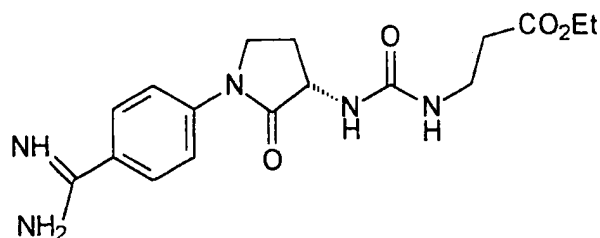
It is also known that another large glycoprotein named fibronectin, which is a major extracellular matrix protein, interacts with platelets. Various relatively large polypeptide fragments in the cell-binding domain of fibronectin have been found to have cell-attachment activity. Certain relatively short peptide fragments from the same molecule were found to promote cell

- 5 attachment to a substrate when immobilized on the substrate or to inhibit attachment when in a solubilized or suspended form.

US 5,721,366 is directed to a class of compounds of the formula

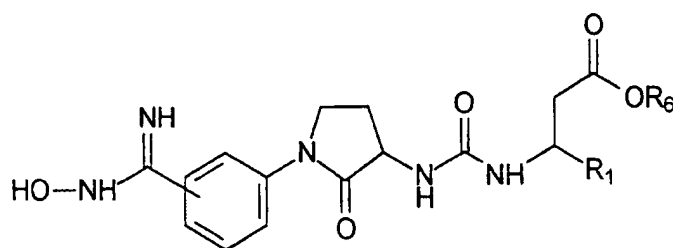


10 which are useful as modulators and/or inhibitors of platelet aggregation. Included in this class of compounds is a compound of the formula



15 generically known as orbofiban, chemically known as N-[[[1-[4-(aminoiminomethyl)phenyl]-2-oxopyrrolidin-3S-yl]amino]carbonyl]-β-alanine.

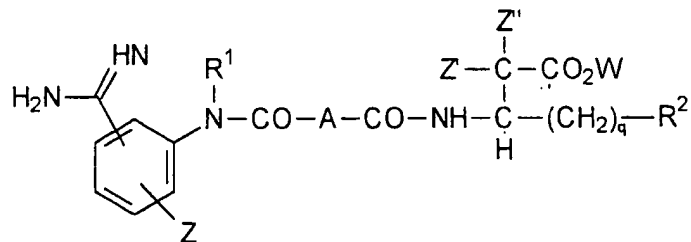
US 5,610,296 discloses compounds of the formula



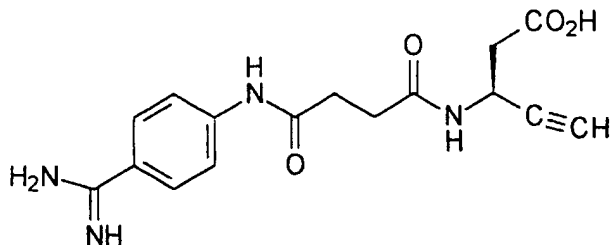
20 wherein R<sub>1</sub> is selected from the group consisting of H, lower alkyl, and aryl; and

- 5 wherein R<sub>6</sub> is selected from the group consisting of lower alkyl, aryl, arylalkyl and acyloxymethyl.

US 5,344,957 is directed to GP IIb/IIIa antagonists of the formula



- 10 which are useful as modulators and/or inhibitors of platelet aggregation. Included in this class of compounds is a compound of the formula



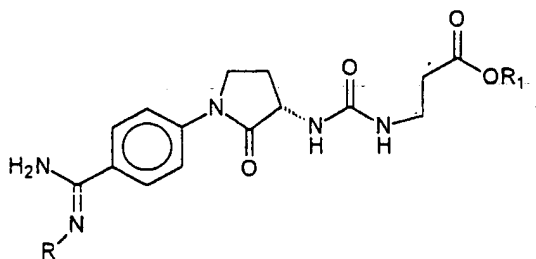
generically known as xemilofiban and chemically known as ethyl 3S-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]amino]-4-pentynoate.

- 15 Bioconversion of amidoxime prodrugs to amidines has been disclosed and occurs via hepatic metabolism [Hauptmann, J. et al. Pharmazie 43, 559-560 (1988)]. European Patent Application 656,348 A2 discloses double prodrugs of a series of glycoprotein IIb/IIIa antagonists. The compounds are further disclosed in Weller, T. et al. J. Med. Chem. 39, 3139-3147 (1996).

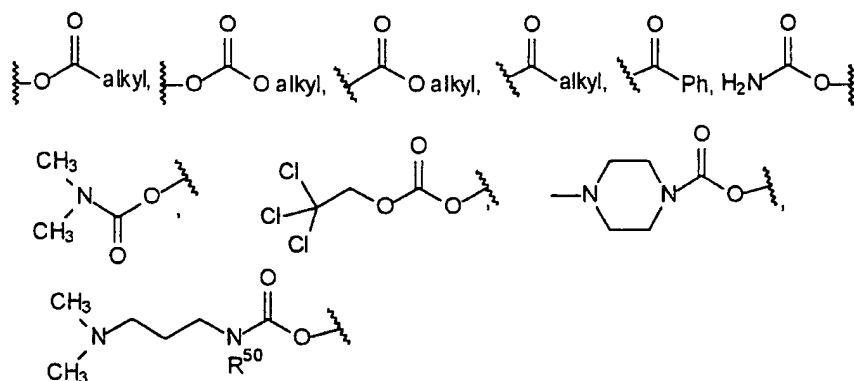
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#### Summary of the Invention

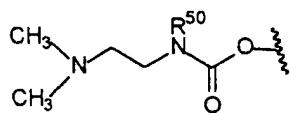
The present invention relates to double prodrugs of pharmacologically active glycoprotein IIb/IIIa antagonists of the formula



wherein  $R_1$  is selected from the group consisting of lower alkyl of about 2 to about 8 carbon atoms, cycloalkyl, and aralkyl;  $R$  is selected from the group consisting of alkoxy,

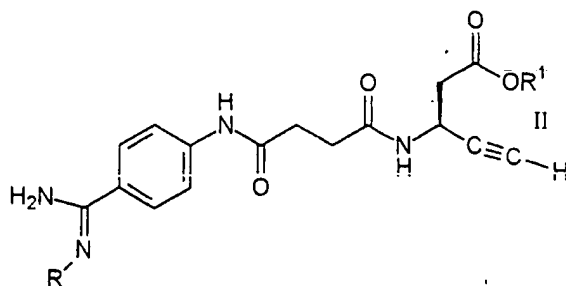


wherein  $R^{50}$  is H or alkyl; and



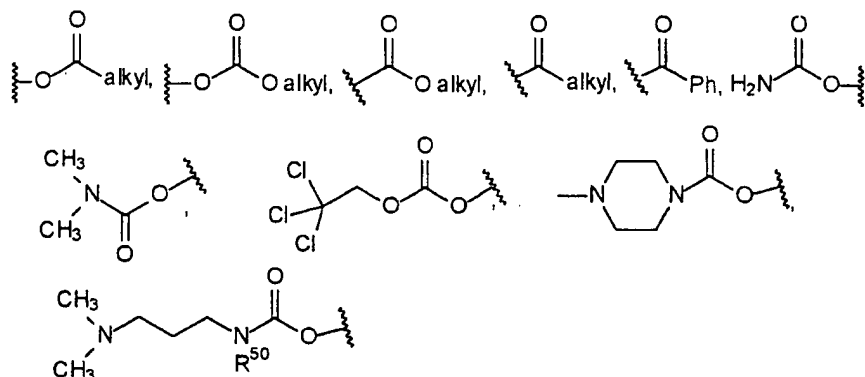
wherein  $R^{50}$  is H or alkyl; and pharmaceutically acceptable salts thereof.

In another embodiment the present invention relates to double prodrugs of pharmacologically active glycoprotein IIb/IIIa antagonists of the formula

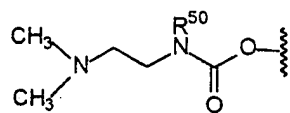


5

wherein  $R_1$  is selected from the group consisting of H, lower alkyl of about 2 to about 8 carbon atoms, cycloalkyl and aralkyl; R is selected from the group consisting of OH, alkoxy,



10 wherein  $R^{50}$  is H or alkyl; and



wherein  $R^{50}$  is H or alkyl; and pharmaceutically acceptable salts thereof.

It is another object of the invention to provide pharmaceutical compositions comprising compounds of the formulae I and II. Such compounds and compositions have usefulness as modulators and/or inhibitors of platelet aggregation. The invention also relates to a method of therapeutically inhibiting or modulating platelet aggregation in a mammal in need of such treatment.

15

5

Detailed Description of the Invention

The present invention relates to compounds of the formula I and formula II or pharmaceutically acceptable salts thereof.

Preferred embodiments exemplifying the invention are the following compounds:

10

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester monohydrochloride;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine methyl ester;

15

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine 1-methylethyl ester monohydrochloride;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine propyl ester monohydrochloride;

20

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine 2-methylpropyl ester monohydrochloride;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine butyl ester monohydrochloride;

25

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester;

30

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine phenylmethyl ester monohydrochloride monohydrate;



5 N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-  
amino]carbonyl]-β-alanine pentyl ester monohydrochloride;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-  
amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

10

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)-carbonyl]oxy]amino]-  
methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

15

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester  
monohydrochloride;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-  
oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

20

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
methyl ester monohydrochloride;

25

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-  
methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
ethyl ester dihydrochloride;

30

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester dihydrochloride;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester monoacetate;

5

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine ethyl ester dihydrochloride;

10

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester dihydrochloride;

15

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester dihydrochloride;

20

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester monoacetate;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester monohydrate;

25

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester dihydrochloride;

30

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester dihydrochloride;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl

- 5 ester monoacetate monohydrate;
- N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;
- 10 N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl  
ester dihydrochloride;
- N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-  
15 methylpropyl ester dihydrochloride;
- N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-  
methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2-methylpropyl ester dihydrochloride;
- 20 N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2-methylpropyl ester dihydrochloride;
- 25 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2-methylpropyl ester monoacetate;
- N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-  
30 2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;
- N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-  
methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine

5 butyl ester dihydrochloride;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester dihydrochloride;

10 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-  
oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester dihydrochloride;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-  
methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-  
15 alanine 2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester;

20 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2,2-dimethylpropyl ester dihydrochloride;

25 N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

30 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-  
oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-

5           phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine cyclohexyl  
                  ester dihydrochloride monohydrate;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
                  2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine cyclohexyl ester;

10

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
                  2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine cyclohexyl  
                  ester monoacetate monohydrate;

15       N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-  
                  phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine  
                  pentyl ester dihydrochloride;

20       N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
                  2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine pentyl ester monohydrate;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
                  2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine pentyl ester;

25       N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-  
                  methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine  
                  1,1-dimethylethyl ester dihydrochloride;

30       N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-  
                  2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1,1-dimethylethyl  
                  ester dihydrochloride;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-

5 2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1,1dimethylethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]imino-methyl]-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine methyl ester;

10 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]-  
phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine ethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester;

15 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester;

20 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine butyl ester;

25 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2,2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine phenylmethyl ester;

30 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine pentyl ester;

5 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine methyl ester;

10 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine ethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester;

15 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-  
20 pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester;

25 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine butyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-  
pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2,2-dimethylpropyl ester;

30 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-  
pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine phenylmethyl ester;

5 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

10 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]-amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine mono(trifluoroacetate);

15 N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine bis(trifluoroacetate) monohydrate;

20 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine monohydrate;

25 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

30 N-[[[(3S)-1-[4-[imino[(methoxycarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester hydrochloride;

N-[[[(3S)-1-[4-[imino[(methoxycarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;



5

N-[[[(3S)-1-[4-[(acetyloxy)amino]iminomethyl]phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

10

N-[[[(3S)-1-[4-[(ethoxycarbonyloxy)amino]imino-methyl]phenyl]-2-  
oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester; and

15

N-[[[(3S)-1-[4-[imino[(2,2,2-trichloroethoxy)carbonyloxy]-  
amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
carbonyl]-β-alanine ethyl ester.

The invention further relates to pharmaceutical compositions  
containing therapeutically effective amounts of the compounds of Formula I or  
II and more preferably the compounds listed above.

Such compounds are double prodrugs of the pharmacologically active  
glycoprotein IIb/IIIa antagonists, orbofiban and xemilofiban. Such compounds  
are designed to improve the oral bioavailability and in particular the  
pharmacodynamic/pharmacokinetic (PK/PD) properties of the active agents.  
Bioactivation of such double prodrugs to the pharmacologically active agent  
will occur through a combination of hepatic metabolism and plasma ester  
hydrolysis. The compounds of this invention are intended to influence oral  
bioavailability and the PK/PD properties associated with the formation and  
elimination of the active agent by modulating the rate of bioactivation of the  
double prodrug.

As used herein, the term "alkyl" refers to a straight chain or branched  
chain hydrocarbon radical having from 2 to 8 carbon atoms. Examples of  
such alkyl radicals are ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-  
butyl, pentyl, neopentyl, hexyl, isohexyl, n-octyl and the like.

5           As used herein the term "alkylene" or "lower alkylene" refers to divalent linear or branched saturated hydrocarbon radicals of 1 to about 8 carbon atoms.

          As used herein, the term "alkoxy" includes straight or branched chain oxy containing radicals of the formula  $-OR_4$  wherein  $R_4$  is an alkyl moiety as  
10       defined above. Examples of such groups are methoxy, ethoxy, n-propoxy, n-butoxy, isobutoxy, t-butoxy, sec-butoxy, isopropoxy and the like.

          As used herein the terms "halo" or "halogen" refer to a chloro (Cl), fluoro (F), bromo (Br) or iodo (I) radical.

          The term "aryl", as used herein denotes aromatic ring systems  
15       composed of one or more aromatic rings. Preferred aryl groups are those consisting of one, two or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, pyridyl, naphthyl, thiophenyl, furanyl, biphenyl and the like.

          The term "pharmaceutically acceptable carrier", as used herein means  
20       a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

          The terms "arylalkyl" or "aralkyl" refer to radicals of the formula  
25        $\text{---}R^{22}-R^{21}$  wherein  $R^{21}$  is aryl as defined above and  $R^{22}$  is an alkylene as defined above. Examples of aralkyl groups include benzyl, pyridinylmethyl, phenethyl and the like.

          As used herein the term "cycloalkyl" refers to saturated carbocyclic ring systems containing 3 to about 8 carbon atoms. Examples of such ring systems are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

30       The term "composition" as used herein means a product which results from the mixing or combining of more than one element or ingredient.

          The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response

5 of a tissue, system or animal that is being sought by a researcher or clinician.

The following is a list of abbreviations and the corresponding meanings as used interchangeably herein:

$^1\text{H-NMR}$  = proton nuclear magnetic resonance  
10  $\text{AcOH}$  = acetic acid  
 $\text{Bn}$  = benzyl  
 $\text{BOC}$  = tert-butoxycarbonyl  
 $\text{Cat.}$  = catalytic amount  
 $\text{CDI}$  = carbonyldiimidazole  
15  $\text{DMF}$  = N,N-dimethylformamide  
 $\text{DSC}$  = Disuccinimidoyl carbonate  
 $\text{Et}$  = ethyl  
 $\text{EtOAc}$  = ethyl acetate  
 $\text{EtOH}$  = ethanol  
20  $\text{g}$  = gram(s)  
 $\text{GP}$  or  $\text{gp}$  = glycoprotein  
 $\text{HOAc}$  = acetic acid  
 $\text{HPLC}$  = high performance liquid chromatography  
 $\text{i-Pr}$  = isopropyl  
25  $\text{L}$  = liter  
 $\text{Me}$  = methyl  
 $\text{MeOH}$  = methanol  
 $\text{mg}$  = milligram  
 $\text{ml}$  = milliliter  
30  $\text{mL}$  = milliliter  
 $\text{m.p.}$  = melting point  
 $\text{n-Bu}$  = normal butyl  
 $\text{n-C}_5\text{H}_{11}$  = normal pentyl  
 $\text{n-Pr}$  = normal propyl

- 5 Pd/C = palladium on carbon  
Ph = phenyl  
PPP = platelet poor plasma  
PRP = platelet rich plasma  
RPHPLC = reverse phase high performance liquid chromatography  
10 RF1 = Reference Compound 1  
RT = room temperature  
TEAP = tetra-ethyl ammonium phosphate  
t-Bu = tert-butyl  
TFA = trifluoroacetic acid  
15 ② = heating the reaction mixture

The compounds as shown in Formula I and Formula II can exist in various isomeric forms and all such isomeric forms are meant to be included. Tautomeric forms are also included as well as pharmaceutically acceptable  
20 salts of such isomers and tautomers.

In the structure and formulas herein, a bond drawn across a bond of a ring can be to any available atom on the ring.

The term "pharmaceutically acceptable salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally  
25 considered suitable for human consumption. Examples of pharmacologically acceptable salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, and tartrate salts. All of the pharmacologically acceptable salts may be prepared by conventional means. (See Berge et al., *J. Pharm. Sci.*, 66(1), 1-  
30 19 (1977) for additional examples of pharmaceutically acceptable salts.)

This invention also relates to a method of inhibiting platelet aggregation and more specifically, a method of treatment involving the administration of compounds of Formula I or Formula II together with pharmaceutically acceptable carriers to achieve such inhibition.

5 For the inhibition of platelet aggregation, compounds of the present invention may be administered orally, parenterally, or by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes, for example, subcutaneous, intravenous, 10 intramuscular, intrasternal, infusion techniques or intraperitoneally.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention 15 required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art using standard preclinical and clinical approaches in the medicinal arts.

Accordingly, the invention provides a class of novel pharmaceutical compositions comprising one or more compounds of the present invention in 20 association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients.

The dosage regimen for treating a condition with the compounds and/or compositions of this invention is based on a variety of factors, 25 including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions.

30 For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. These may contain, for example, an amount of active ingredient from about 1 to 500 mg,

5 preferably from about 25 to 350 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose would typically be about 0.01 to 10  
10 mg/kg body weight injected per day in multiple doses depending on the condition being treated.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch  
15 powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved  
20 in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

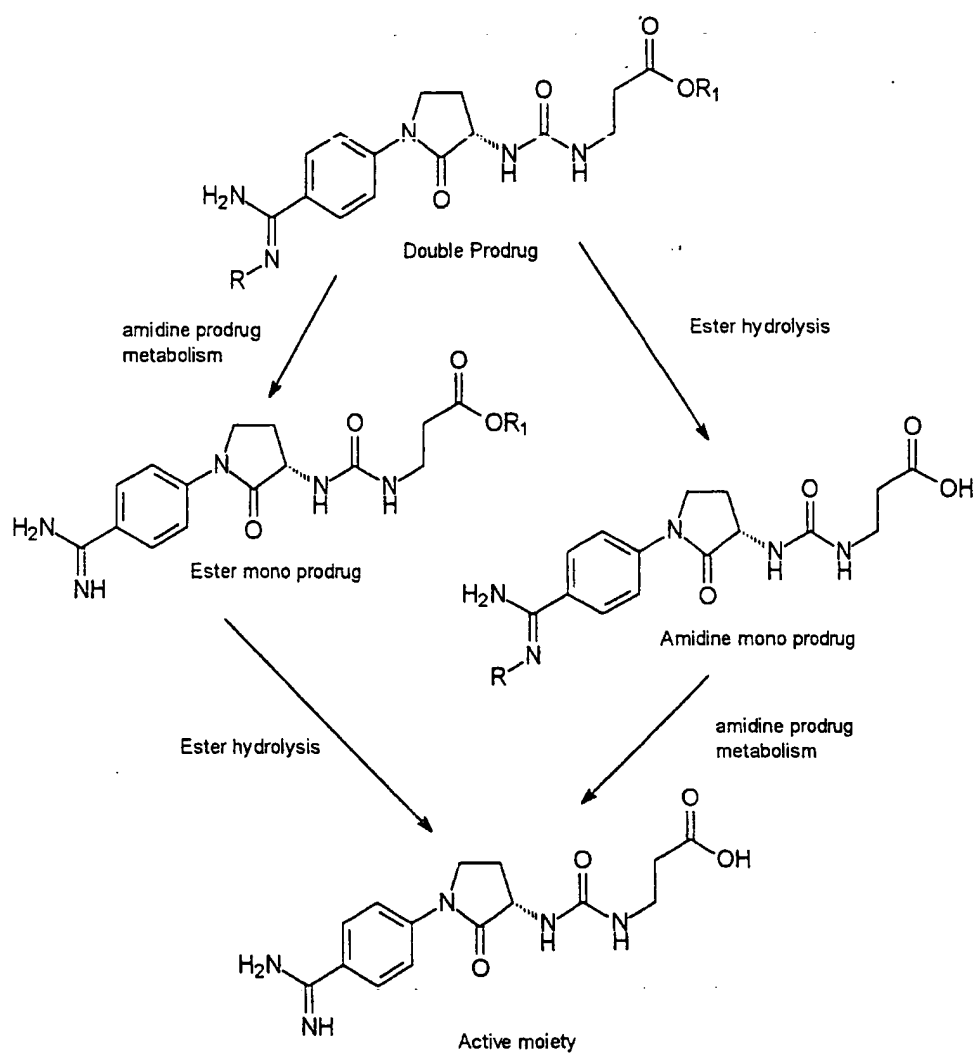
The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid form such as solutions,  
25 suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

30 Scheme A illustrates the metabolic fate of the double prodrug and mono prodrug intermediates leading to the active agent. By either metabolic route, it has been found that the rate of amidine prodrug metabolism can be altered by the nature of the functional group attached to it. By altering the

- 5 functional group, the rate of peak plasma concentration and rate of apparent elimination of the active principle can be manipulated.

5

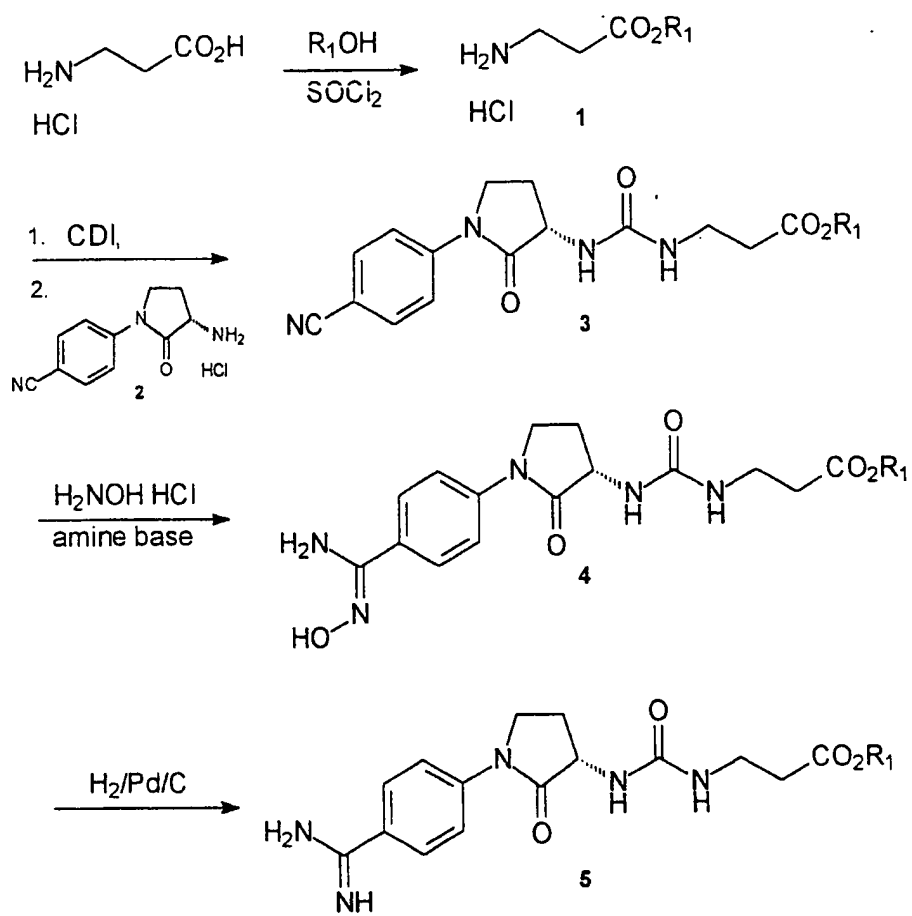
## Scheme A





5           Schemes I-VI which follow are illustrative of methodology for preparing  
the compounds of the present invention.

5

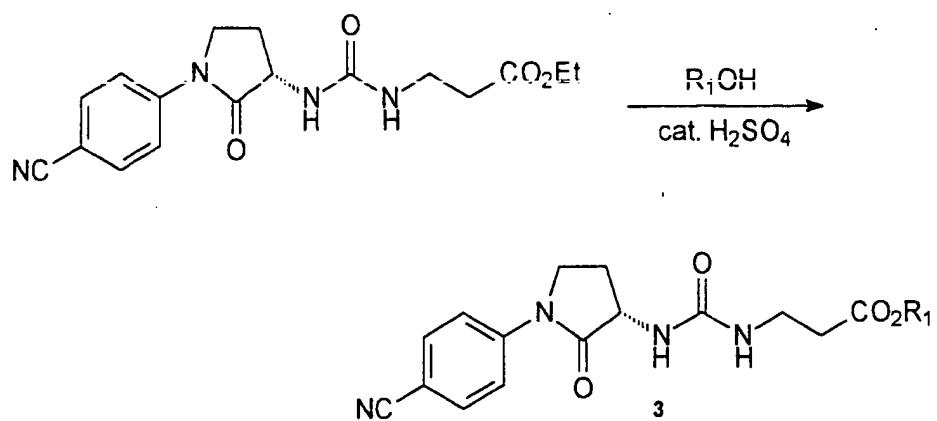
Scheme I

5           The general synthetic method for preparation of compounds of the formula I is outlined in Scheme I. In addition to commercially available beta-alanine esters, other esters are prepared by treating beta-alanine with thionyl chloride in the appropriate alcohol solvent. The corresponding ester hydrochloride **1** is coupled to the lactam **2** by the method described in US

10 5,576,447, whereby the beta-alanine ester is treated with 1,1'-carbonyldiimidazole (CDI) followed by subsequent treatment with **2** in the presence of an appropriate amine base (e.g. triethylamine, diisopropylethylamine). The preparation of lactam **2** is described in US

15 5,576,447. Treatment of the resulting urea, **3**, with hydroxylamine hydrochloride and an appropriate amine base in an alcohol solvent afforded the amidoxime **4**. Catalytic hydrogenation of **4** using a palladium catalyst affords the amidine **5**.

5

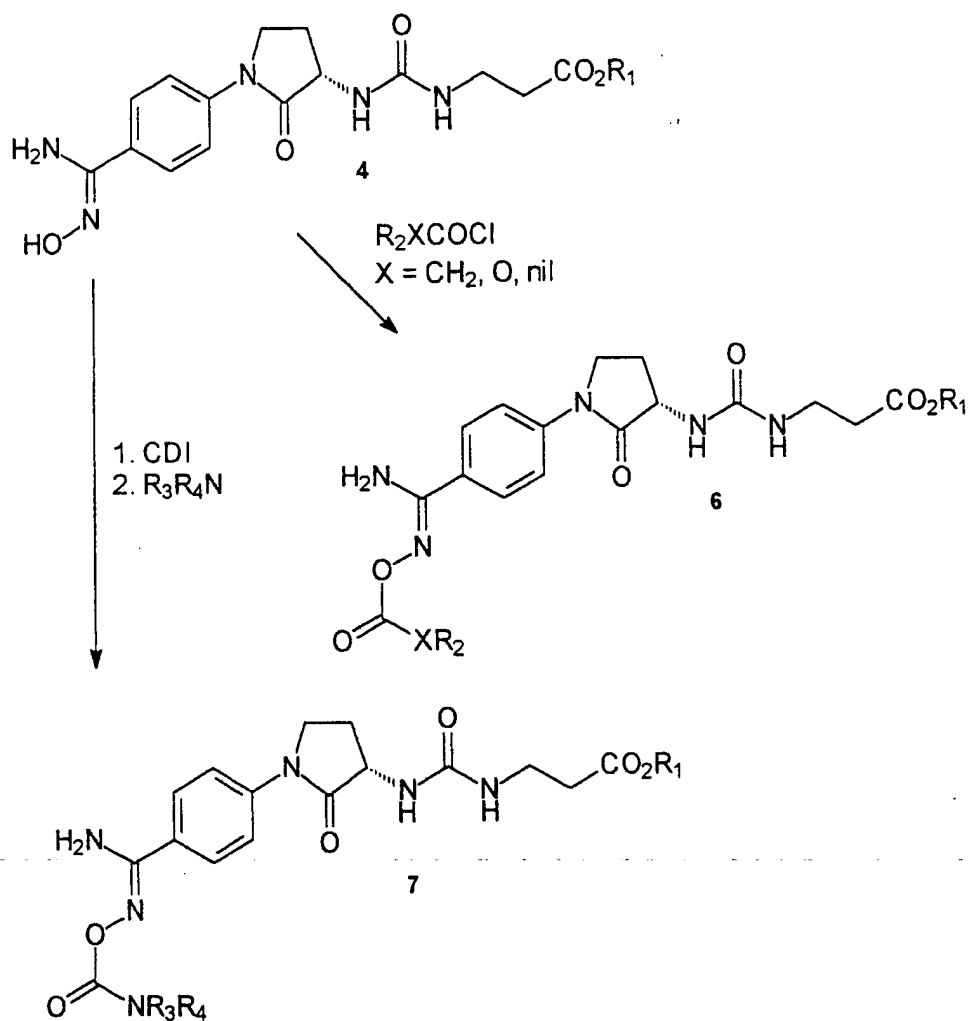
Scheme II

5           An alternative route to **3** is outlined in Scheme II. Transesterification of the ethyl ester (prepared according to the method described in US 5,576,477) in an appropriate alcohol solvent in the presence of catalytic H<sub>2</sub>SO<sub>4</sub> gives the corresponding ester.

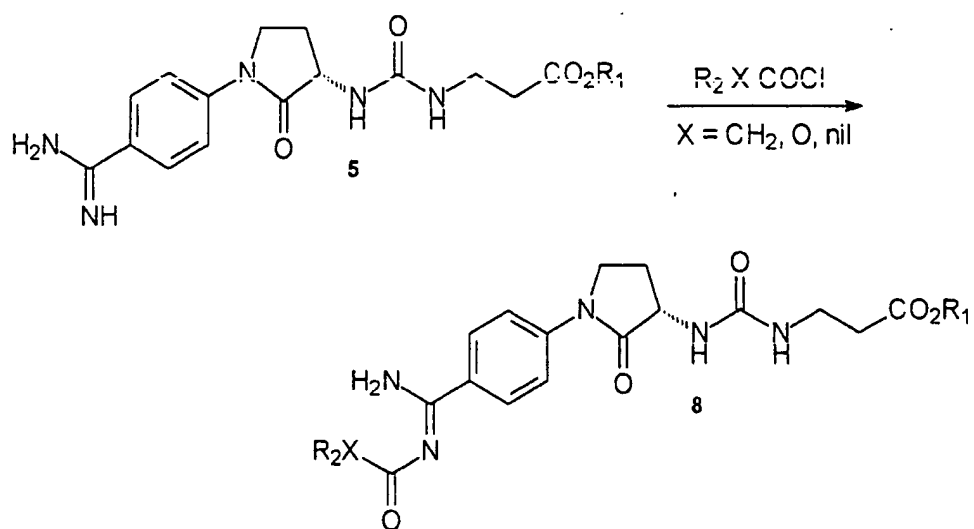
10

5

## Scheme III



5

Scheme IV

5 Both compounds **4** and **5** can be functionalized according to the methodology outlined in Schemes III and IV. Amidoxime **4** is treated with an appropriate acid chloride or chloroformate and an amine base to give the corresponding amidoxime ester or carbonate **6**. Alternatively, **4** is treated with CDI followed by an appropriate primary or secondary amine to give the  
10 corresponding amidoxime carbamate **7**.

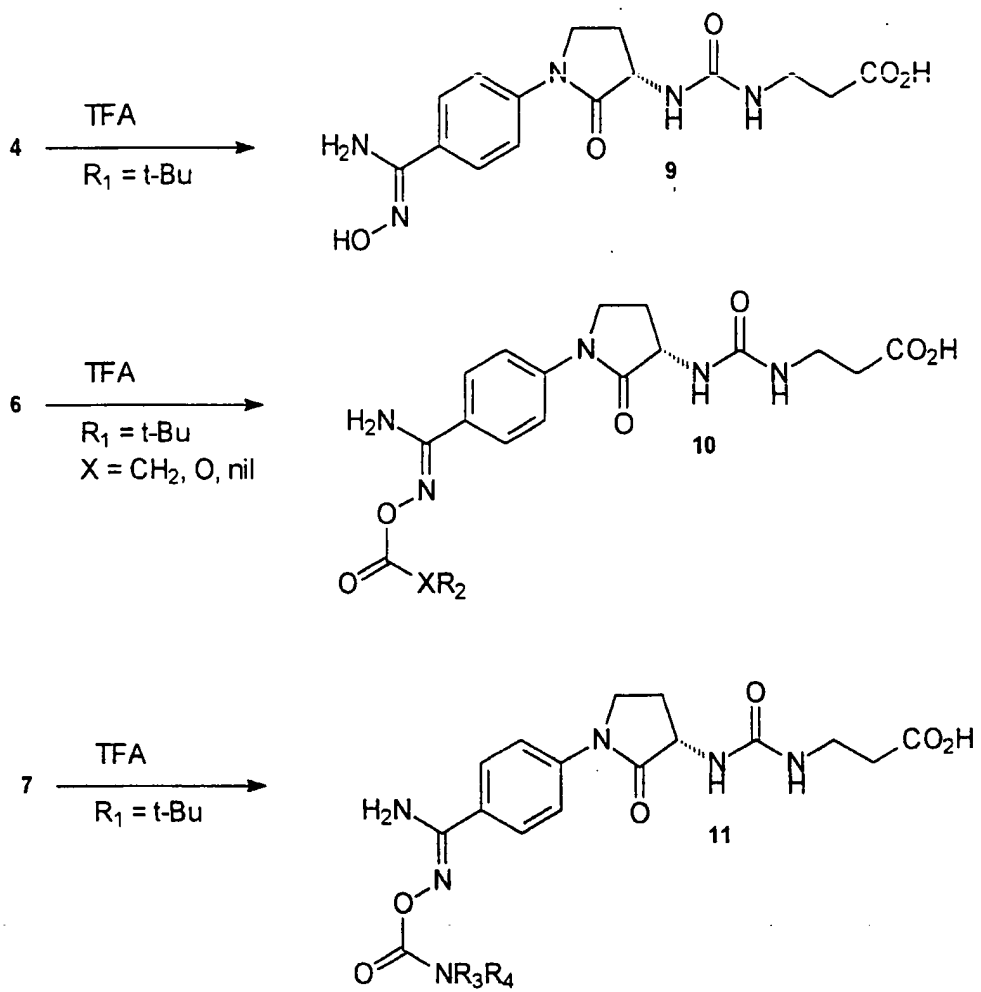
The amidine **5**, in a mixed aqueous/organic medium and an appropriate base (amine base or sodium bicarbonate), when treated with an acid chloride or chloroformate forms the corresponding amidine amide or amidine carbamate **8**.

15



5

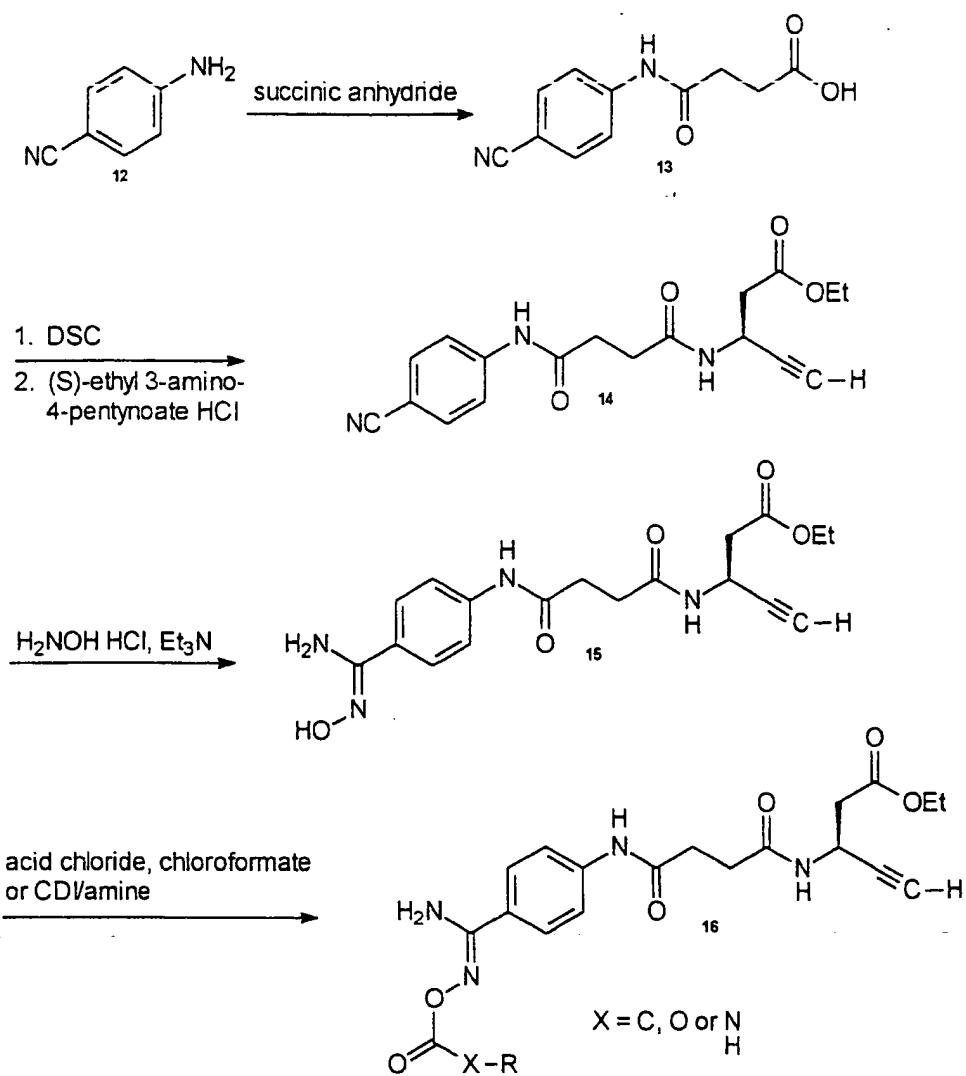
## Scheme V



5            Functionalized amidine free acids are prepared according to the method outlined in Scheme V. Compound **4** ( $R_1 = t\text{-butyl}$ ) is treated with trifluoroacetic acid (TFA) to produce the free acid **9**. Alternatively, compounds **6** and **7** ( $R_1 = t\text{-butyl}$ ) are treated in a similar manner to produce the corresponding free acids **10** and **11**.

5

## Scheme VI



5           Xemilofiban can be prepared according to the methodology disclosed in U.S. 5,344,957. The direct amidine double prodrugs of xemilofiban can be prepared by methodology similar to that disclosed in Scheme IV. The synthesis of the amidoxime double prodrug and functionalized amidoxime double prodrugs can be prepared by the method outlined in Scheme VI.

10          Condensation of 4-aminobenzonitrile **12** with succinic anhydride can afford the hemiacid **13**. Activation of the acid for amide coupling with DSC can form the O-hydroxysuccinimide ester. In situ condensation of this ester with an appropriate  $\beta$ -alanine ester such as (S)-ethyl 3-amino-4-pentynoate HCl in the presence of a tertiary amine base can provide the nitrile ester **14**. Addition of

15          hydroxylamine to the nitrile can provide the amidoxime double prodrug **15**. Further functionalization of the amidoxime with acid chlorides, chloroformates, or amines (after activation of the amidoxime with CDI) can provide a more elaborated series of double prodrugs such as **16**.

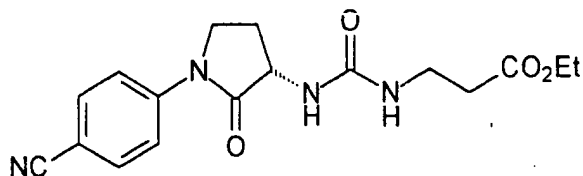
            The following Examples are provided to illustrate the present invention

20          and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the present invention.

5

Example A

Preparation of 3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]-amino]carbonyl]amino]propionate ethyl ester



10 To a suspension of 1,1'-carbonyldiimidazole (572 mg, 3.55 mmol) in pyridine (2.5 mL) at 5°C under nitrogen was added solid ethyl 3-amino-propionate hydrochloride (545 mg, 3.55 mmol). The resulting solution was stirred at 5°C for 15 minutes, diluted with DMF (2.5 mL) and removed from the ice bath. 1-(4-Cyanophenyl)-3(S)-aminopyrrolidin-2-one hydrochloride (700  
15 mg, 2.96 mmol) was added all at once and the reaction mixture was stirred at 75-80°C for 2 hours. After cooling to room temperature, the resulting solution was diluted with 1 N HCl (15 mL). The white precipitate was filtered, washed with H<sub>2</sub>O and dried. Trituration and filtration from methyl t-butyl ether afforded the product (844 mg) (m.p. 168.5-169°C). Extractive work up of the filtrate  
20 with EtOAc afforded additional product (110 mg, 94% yield overall).  
[α]<sub>D</sub><sup>25</sup> = +9.5 (MeOH, c=9.45 mg/mL)

Analysis calculated. for C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>: C, 59.29; H, 5.85; N, 16.27.

Found: C, 58.94; H, 5.71; N, 16.13.

25 The following compounds were obtained analogously by substituting the appropriate beta alanine ester:

5     Example A (a)

3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]-  
amino]propionate 1-methylethyl ester.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.22 (d, J = 7 Hz, 3H), 1.23 (d, J = 7 Hz, 3H), 2.05, (m, 1H),  
2.51 (t, J = 7 Hz, 2H), 2.82 (m, 1H), 3.48 (q, J = 7 Hz, 2H), 3.83 (m, 2H), 4.53  
10 (m, 1H), 4.92 (hept, J = 7 Hz, 2H), 5.52 (m, 2H), 7.67 (d, J = 9 Hz, 2H), 7.81  
(d, J = 9 Hz, 2H).

Example A (b)

3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]amino]-  
15 propionate propyl ester.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.94 (t, J = 7 Hz, 3H), 1.65 (m, 4H), 2.05 (m, 1H), 2.55 (t, J  
= 7 Hz, 2H), 2.83 (m, 1H), 3.49 (q, J = 7 Hz, 2H), 3.85 (m, 2H), 4.05 (t, J = 7  
Hz, 2H), 4.50 (m, 1H), 5.30 (d, J = 7 Hz, 1H), 5.37 (t, J = 7 Hz, 1H), 7.67 (d, J  
= 9 Hz, 2H), 7.81 (d, J = 9 Hz, 2H).

20

Example A (c)

3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]amino]-  
propionate cyclohexyl ester.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.15-1.90 (m, 10H), 2.05 (m, 1H), 2.53 (t, J = 7 Hz, 2H),  
25 2.80 (m, 1H), 3.48 (q, J = 7 Hz, 2H), 3.85 (m, 2H), 4.53 (m, 1H), 4.74 (m, 1H),  
5.57 (m, 2H), 7.67 (d, J = 8 Hz, 2H), 7.81 (d, J = 8 Hz, 2H).

Example A (d)

3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]-  
30 amino]propionate 1,1-dimethylethyl ester.

<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 1.40 (s, 9H), 1.90 (m, 1H), 2.32 (t, J = 7 Hz, 2H), 2.30-  
2.46 (m, 1H), 3.18 (br. t, J = 7 Hz, 2H), 3.70-3.85 (m, 2H), 4.43 (m, 1H), 6.15  
(br. s, 1H), 6.50 (br. d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz,  
2H).

5     Example A (e)

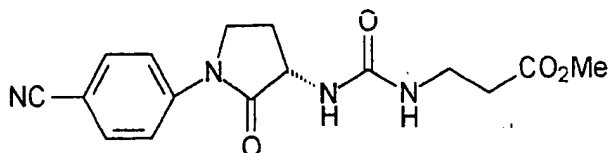
3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]-  
amino]propionate phenylmethyl ester.

<sup>1</sup>H-NMR (d<sub>6</sub>-DMSO) δ 1.93 (m, 1H), 2.40 (m, 1H), 2.52 (t, J = 7 Hz, 2H), 3.28  
(q, J = 7 Hz, 2H), 3.70-3.85 (m, 2H), 4.45 (m, 1H), 5.11 (s, 2H), 6.25 (t, J = 7  
10 Hz, 1H), 6.50 (d, J = 7 Hz, 1H), 7.30-7.40 (m, 5H), 7.86 (d, J = 9 Hz, 2H), 7.90  
(d, J = 9 Hz, 2H).

5

Example B

Preparation of 3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]-amino]carbonyl]amino]propionate methyl ester



10 To a stirred solution of the product of Example A (10.1 g, 29.2 mmol) in MeOH (60 mL) was added concentrated sulfuric acid (0.5 mL). The reaction mixture was heated to 50°C and stirred overnight. After cooling to room temperature, the reaction mixture was diluted with diethyl ether. The resulting precipitate was filtered, washed with EtOH:H<sub>2</sub>O (9:1) and dried affording the  
15 product (9.0 g, 93% yield).

<sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) δ 1.90 (m, 1H), 2.32-2.50 (m, 3H), 3.23 (q, J = 7 Hz, 2H), 3.59 (s, 3H), 3.68-3.83 (m, 2H), 4.43 (m, 1H), 6.20 (t, J = 7 Hz, 1H), 6.45 (d, J = 8 Hz, 1H), 7.83 (d, J = 10 Hz, 2H), 7.88 (d, J = 10 Hz, 2H).

20 The following compounds were obtained analogously by substituting for the appropriate alcohol:

Example B (a)

25 3-[[[1-(4-cyanophenyl)-2-oxo-3(S)-pyrrolidinyl]amino]carbonyl]amino]-propionate 2,2-dimethylpropyl ester.

The reaction was carried out as above except THF was used as a co-solvent.

<sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) δ 0.88 (s, 9H), 1.90 (m, 1H), 2.31-2.50 (m, 3H), 3.24 (t, 7 Hz, 2H), 3.72-3.83 (m, 4H), 4.42 (m, 1H), 6.15 (br. m, 1H), 6.42 (br. m, 1H), 7.83 (d, J = 9 Hz, 2H), 7.89 (d, J = 9 Hz, 2H).

30

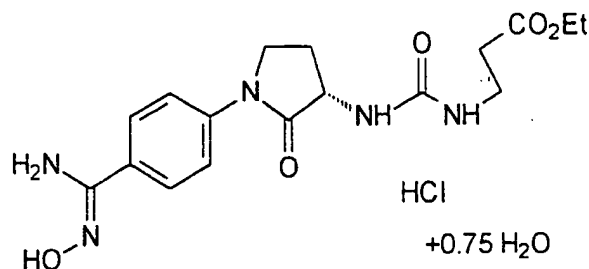




5

Example 1

Preparation of N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester monohydrochloride



10

To a suspension of the product of Example A (5.7 g, 16.4 mmol) and hydroxylamine hydrochloride (5.7 g, 82.3 mmol) in EtOH (50 mL) was added triethylamine (8.3 g, 82.3 mmol). The reaction mixture was heated to 60-65°C and stirred for 3 hours. The reaction mixture was concentrated under reduced pressure and diluted with H<sub>2</sub>O. The precipitate was filtered, washed with H<sub>2</sub>O and dried affording the product (5.4 g) as the free base. The product was taken up in dilute HCl and purified by RPHPLC affording the product as the hydrochloride salt as a lyophilized powder (5.4 g).

15

Analysis calculated. for C<sub>17</sub>H<sub>23</sub>N<sub>5</sub>O<sub>5</sub>·HCl·3/4H<sub>2</sub>O:

20

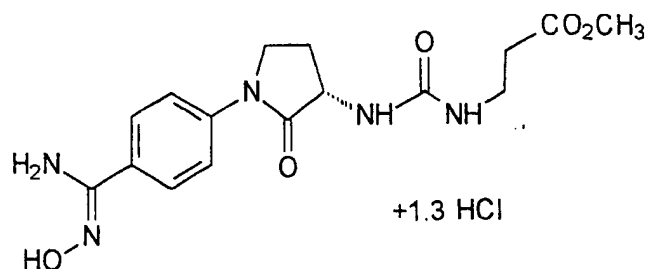
C, 47.78; H, 6.01; N, 16.39.

Found: C, 47.89; H, 6.09; N, 16.25.

The following compounds were obtained analogously:

5 Example 1 (a)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine methyl ester



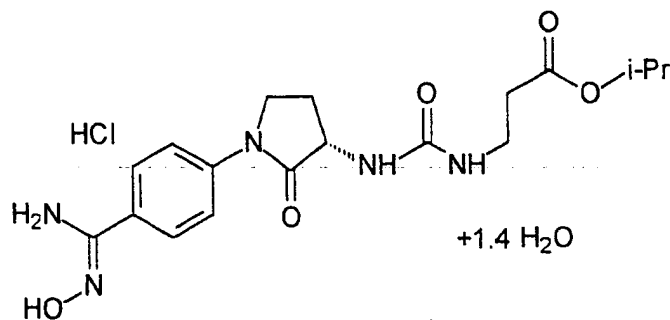
10 m. p. 197-205°C (dec.).

Analysis calculated. for  $C_{16}H_{21}N_5O_5 \cdot 1.3HCl$ : C, 46.78; H, 5.47; N, 17.05.

Found: C, 46.78; H, 5.65; N, 17.21.

Example 1 (b)

15 N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine 1-methylethyl ester monohydrochloride



m. p. 157-162°C (dec.).

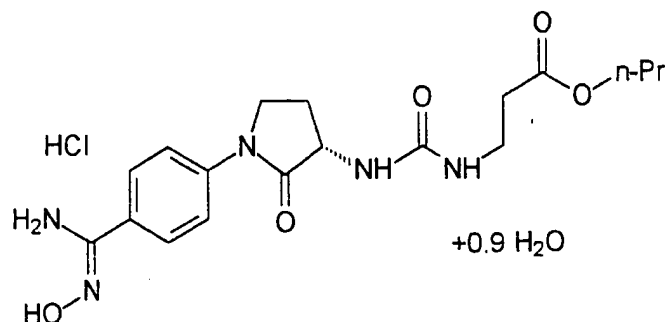
20 Analysis calculated. for  $C_{18}H_{25}N_5O_5 \cdot 1.0HCl \cdot 1.4 H_2O$ :

C, 47.71; H, 6.41; N, 15.46.

Found: C, 47.79; H, 6.13; N, 15.34.

5     Example 1 (c)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine propyl ester monohydrochloride



10     m. p. 163-165°C (dec.).

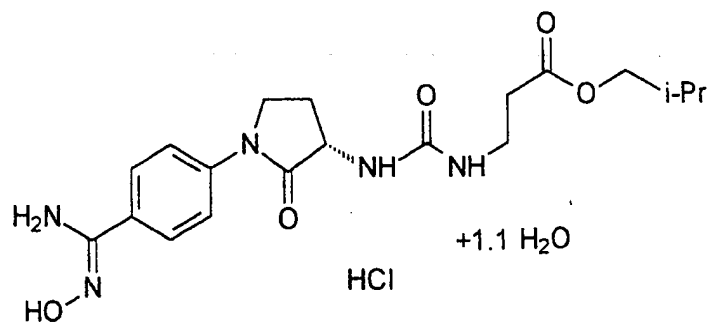
Analysis calculated for C<sub>19</sub>H<sub>27</sub>N<sub>5</sub>O<sub>5</sub>·1.0HCl·0.9H<sub>2</sub>O:

C, 48.68; H, 6.31; N, 15.77.

Found: C, 48.74; H, 5.99; N, 15.71.

15     Example 1 (d)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine 2-methylpropyl ester monohydrochloride



20     <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 0.88 (d, J = 8 Hz, 6H), 1.8-2.0 (m, 2H), 2.3-2.5 (m, 1H),  
2.43 (t, J = 7 Hz, 2H), 3.23(m, 2H), 3.76 (m, 2H), 3.81 (d, J = 7 Hz, 2H), 4.43  
(m, 1H), 6.22 (m, 1H), 6.51 (d, J = 7 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.89 (d, J  
= 8 Hz, 2H), 9.0 (br s, 2H), 11.03 (s, 1H).

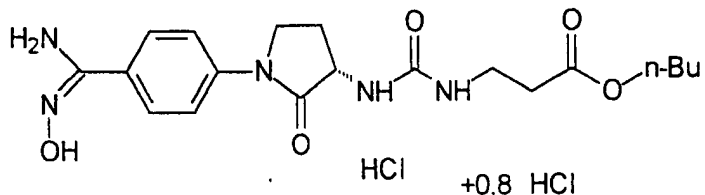
5 Analysis calculated for  $C_{19}H_{27}N_5O_5 \cdot 1.0 \text{ HCl} \cdot 1.1 \text{ H}_2\text{O}$ :

C, 49.42; H, 6.59; N, 15.17.

Found: C, 49.17; H, 6.28; N, 15.01.

Example 1 (e)

10 N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]- $\beta$ -alanine butyl ester monohydrochloride



m. p. 192-193°C (dec.).

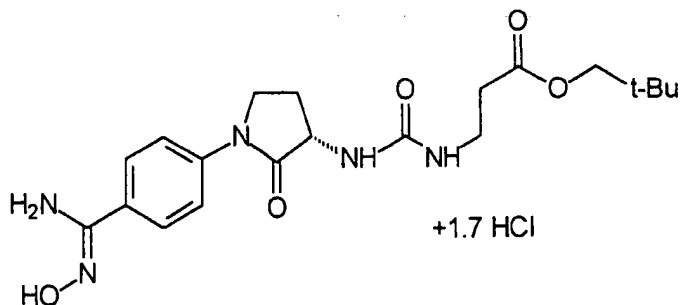
Analysis calculated for  $C_{19}H_{27}N_5O_5 \cdot 1.0 \text{ HCl} \cdot 0.8 \text{ H}_2\text{O}$ :

15 C, 50.11; H, 6.33; N, 15.21.

Found: C, 50.10; H, 6.54; N, 15.35.

Example 1 (f)

20 N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]- $\beta$ -alanine 2,2-dimethylpropyl ester



m. p. 168-170°C (dec.).

Analysis calculated for  $C_{20}H_{29}N_5O_5 \cdot 1.7 \text{ HCl}$ :

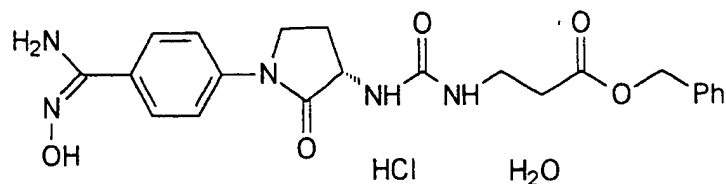
C, 49.89; H, 6.43; N, 14.55.

5

Found: C, 49.92; H, 6.61; N, 14.43.

Example 1 (g)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine phenylmethyl ester monohydrochloride monohydrate



10

m. p. 140-145°C

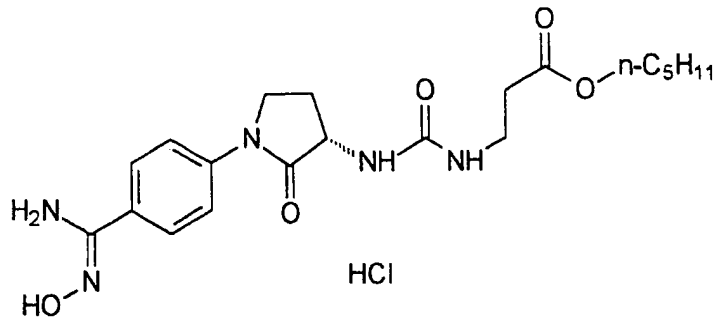
Analysis calculated for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>5</sub>·1.0 HCl: C, 53.50; H, 5.71; N, 14.18.

Found: C, 53.49; H, 5.47; N, 14.09.

15

Example 1 (h)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]-amino]carbonyl]-β-alanine pentyl ester monohydrochloride



20

m. p. 140-145°C

Analysis calculated for C<sub>20</sub>H<sub>29</sub>N<sub>5</sub>O<sub>5</sub>·1.0 HCl·0.8 H<sub>2</sub>O:

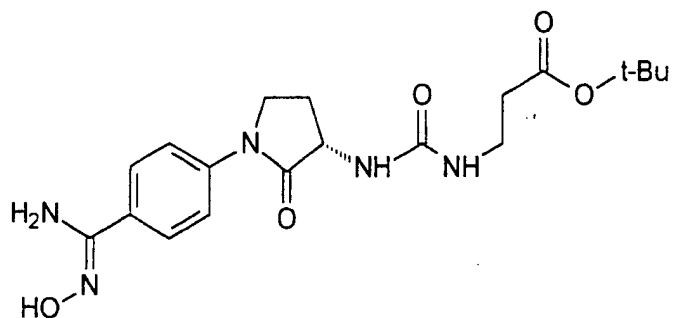
C, 51.07; H, 6.77; N, 14.89.

Found: C, 51.00; H, 6.74; N, 14.64.

25

5     Example 1 (i)

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]-amino]carbonyl]-β-alanine 1,1-dimethylethyl ester

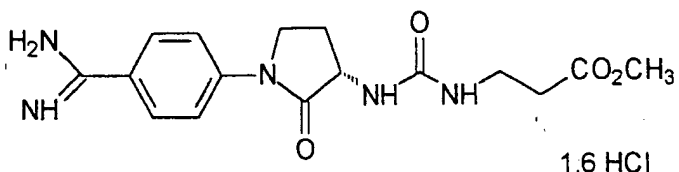


10      $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  1.40 (s, 9H), 1.88 (m, 1H), 2.31 (t,  $J$  = 7 Hz, 2H), 2.35-2.43 (m, 1H), 3.19 (br. t,  $J$  = 7 Hz, 2H), 3.70-3.83 (m, 2H), 4.40 (m, 1H), 5.32 (s, 2H), 6.12 (t,  $J$  = 8 Hz, 1H), 6.47 (d,  $J$  = 8 Hz, 1H), 7.67 (s, 4H), 9.58 (s, 1H).

5

Example 2

Preparation of N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine methyl ester hydrochloride



To a suspension of the product of Example 1a (773 mg, 2.1 mmol) in  
 10 50% aqueous HOAc (20 mL) was added 5% Pd/C (250 mg, 50% wet). The  
 mixture was hydrogenated at 60°C using 60 psi H<sub>2</sub> for 28 hours. The catalyst  
 was filtered and the solvent evaporated under reduced pressure. The residue  
 was taken up in dilute HCl and purified by RPHPLC affording the product (700  
 mg, 82% yield) as the hydrochloride salt after lyophilization [m. p. 208-216°C  
 15 (dec.)].

Analysis calculated for C<sub>16</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>·1.6HCl: C, 47.37; H, 5.61; N, 17.26.

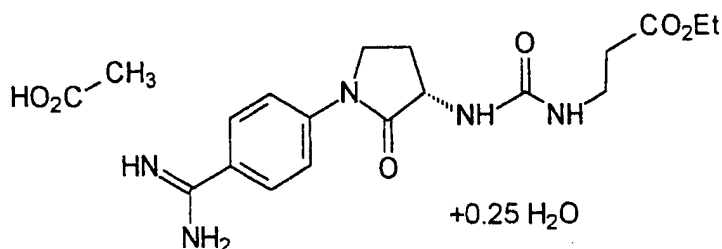
Found: C, 47.05; H, 5.97; N, 17.62.

The following compounds were prepared analogously:

20

Example 2 (a) (RF2)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
 carbonyl]- $\beta$ -alanine ethyl ester acetate



25 The reaction was carried out as above except HOAc was used in the  
 RPHPLC mobile phase.



- 5 m.p. 213-214°C (dec.) Enantiomeric purity was determined by chiral HPLC using a Chiralcel-OD column and EtOH/Heptane/TFA (20:80:0.1) as the mobile phase and was determined to be >99.9% e. e.

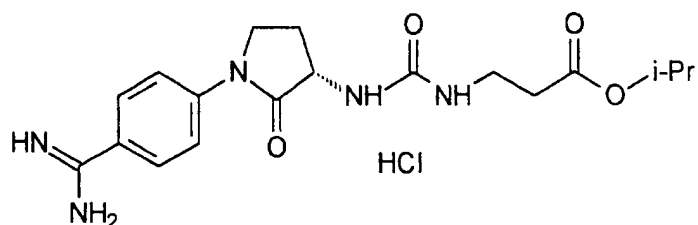
$[\alpha]_D^{25} = +13.2$  (MeOH, c = 9.43 mg/mL)

Analysis calculated for  $C_{19}H_{27}N_5O_6$ : C, 54.15; H, 6.46; N, 16.62.

10 Found: C, 54.08; H, 6.57; N, 16.57.

### Example 2 (b)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-carbonyl]-β-alanine 1-methylethyl ester hydrochloride



15

m. p. 192-193°C (dec.).

Analysis calculated for  $C_{18}H_{25}N_5O_4 \cdot 1.5 \text{ HCl} \cdot 0.5 \text{ H}_2\text{O}$ :

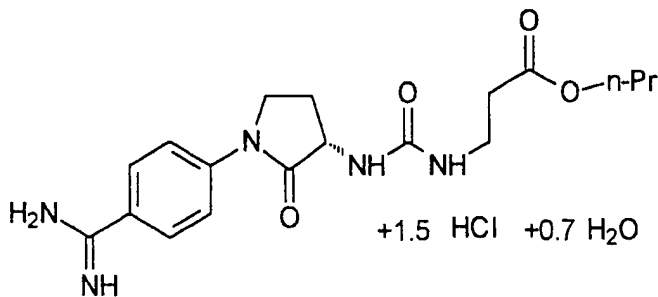
C, 49.23; H, 6.31; N, 15.95.

Found: C, 49.17; H, 6.72; N, 16.09.

20

### Example 2 (c)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-carbonyl]-β-alanine propyl ester



5 m. p. 193-204°C (dec.).

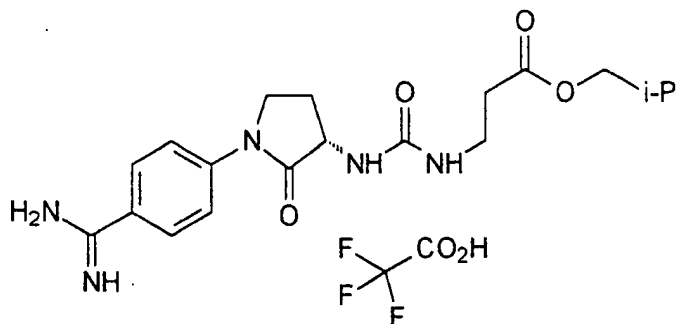
Analysis calculated for  $C_{18}H_{25}N_5O_4 \cdot 1.5 HCl \cdot 0.7 H_2O$ :

C, 48.83; H, 6.35; N, 15.82.

Found: C, 48.95; H, 6.11; N, 15.74.

10 Example 2 (d)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidiny]amino]-  
carbonyl]-β-alanine 2-methylpropyl ester mono(trifluoroacetate)



The reaction was carried out as above except TFA was used in the RPHPLC  
15 mobile phase.

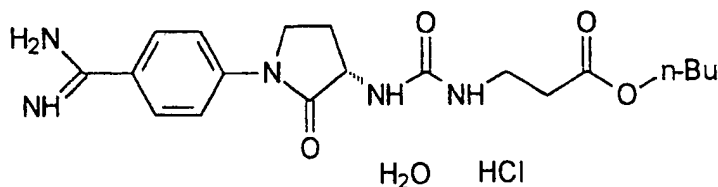
m. p. 193-194°C (dec.)

Analysis calculated for  $C_{19}H_{27}N_5O_4 \cdot 1.0 TFA$ : C, 50.10; H, 5.61; N, 13.91.

Found: C, 49.73; H, 5.54; N, 13.80.

20 Example 2 (e)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidiny]amino]-  
carbonyl]-β-alanine butyl ester monohydrochloride monohydrate



The reaction was carried out as above except HCl was used in the  
25 RPHPLC mobile phase.

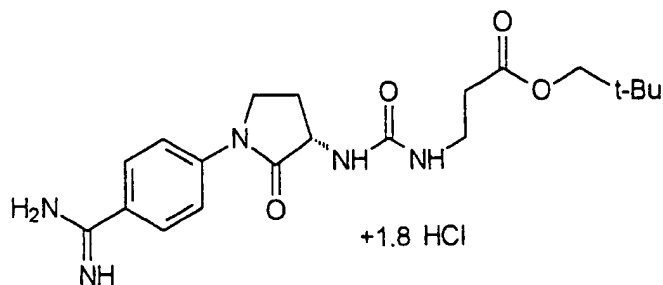
5 m. p. 202-204°C.

Analysis calculated for  $C_{19}H_{27}N_5O_4 \cdot 1.0 \text{ HCl}$ : C, 51.41; H, 6.81; N, 15.68.

Found: C, 51.21; H, 6.65; N, 15.91.

Example 2 (f)

10 N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
carbonyl]-β-alanine 2,2-dimethylpropyl ester hydrochloride



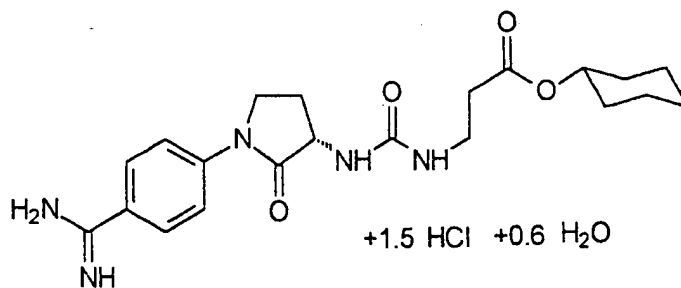
m. p. 203-205°C (dec.).

Analysis calculated for  $C_{20}H_{29}N_5O_4 \cdot 1.8 \text{ HCl}$ : C, 51.21; H, 6.62; N, 14.93.

Found: C, 51.31; H, 6.63; N, 15.27.

Example 2 (g)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
carbonyl]-β-alanine cyclohexyl ester



20 m. p. 197-199°C (dec.).

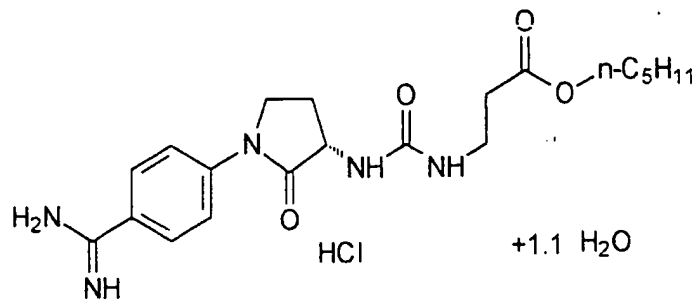
Analysis calculated for  $C_{21}H_{29}N_5O_4 \cdot 1.5 \text{ HCl} \cdot 0.5 \text{ H}_2\text{O}$ :

C, 52.44; H, 6.64; N, 14.56.

Found: C, 52.48; H, 6.45; N, 14.28.

5 Example 2 (h)

N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-carbonyl]-β-alanine pentyl ester monohydrochloride



m. p. 211-212°C.

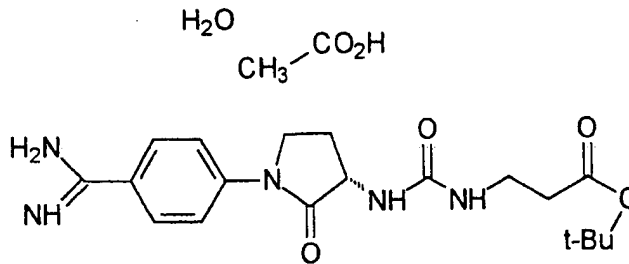
10 Analysis calculated for C<sub>20</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub>·1.0 HCl·1.1 H<sub>2</sub>O:

C, 52.25; H, 7.06; N, 15.23.

Found: C, 52.14; H, 6.85; N, 15.18.

Example 2 (i)

15 N-[[[(3S)-1-[4-(aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-carbonyl]-β-alanine 1,1-dimethylethyl ester acetate



m. p. 188-189°C

Analysis calculated for C<sub>19</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub>·1.1 HOAc·1.0 H<sub>2</sub>O:

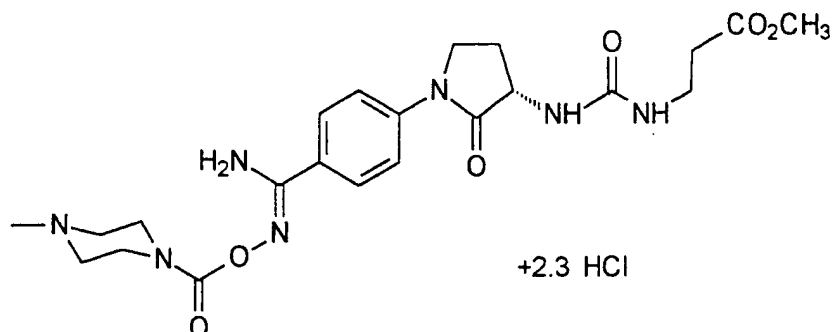
C, 53.77; H, 7.11; N, 14.79.

Found: C, 53.89; H, 6.86; N, 14.45.

5

Example 3

Preparation of N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)-  
carbonyl]oxy]amino]-methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
carbonyl]-β-alanine methyl ester



10

To a room temperature solution of the product of Example 1(a) (533 mg, 1.5 mmol) in DMF (4 mL) was added CDI (238 mg, 1.5 mmol). After 2 hours, to the resulting slurry was added 1-methylpiperazine (147 mg, 1.5 mmol). The resulting clear solution was stirred overnight then diluted with  
15 ether. The white solid was filtered, washed sequentially with ether, cold water ethanol, water/acetonitrile (5:95) then acetonitrile. The resulting solid was dissolved in HCl (0.4 N ) and lyophilized to a dry solid affording the product (665 mg, 79% yield) [m. p. 155-157°C (dec.)].

Analysis calculated for  $C_{22}H_{31}N_7O_6 \cdot 2.3 \text{ HCl}$ : C, 46.08; H, 5.85; N, 17.10.

20

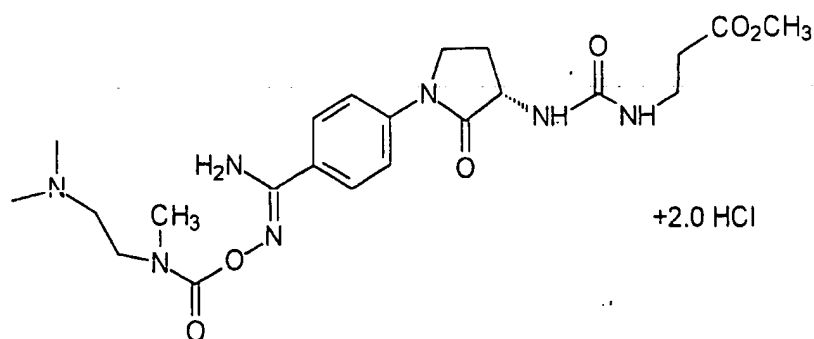
Found: C, 46.03; H, 5.56; N, 16.94.

The following compounds were prepared analogously from the compounds of Example 1 and the appropriate amines:

25

Example 3 (a)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester  
monohydrochloride



5

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

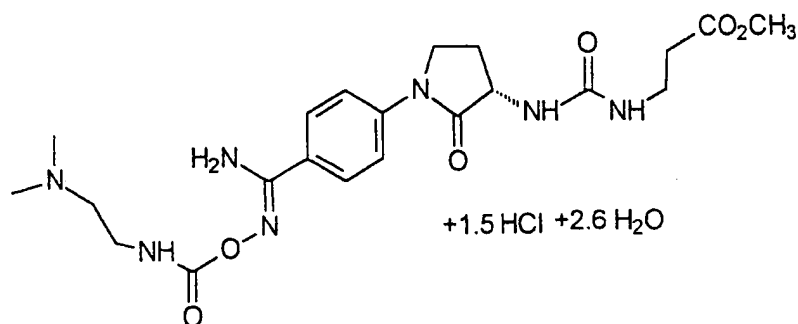
m. p. 145-148°C (dec.).

10 Analysis calculated for  $C_{22}H_{33}N_7O_6 \cdot 2.0 \text{ HCl}$ : C, 46.81; H, 6.25; N, 17.37.  
 Found: C, 46.66; H, 6.49; N, 17.33.

### Example 3 (b)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester

15



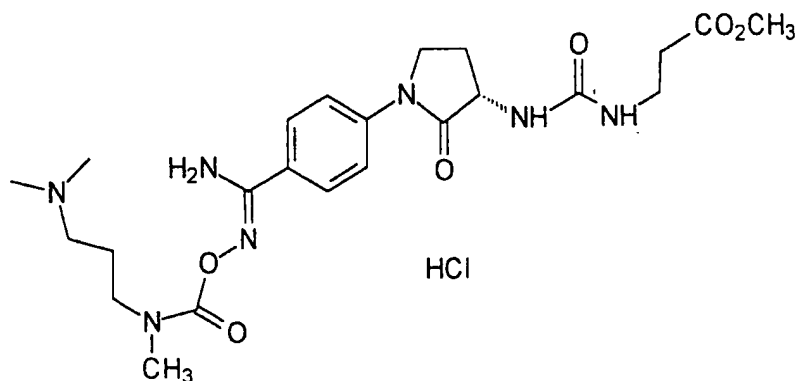
The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 145-152°C (dec.).

20 Analysis calculated for  $C_{21}H_{31}N_7O_6 \cdot 1.5 \text{ HCl} \cdot 2.6 \text{ H}_2\text{O}$ :  
 C, 43.56; H, 6.56; N, 16.93.  
 Found: C, 43.53; H, 6.34; N, 16.98.

5 Example 3 (c)

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester monohydrochloride



10

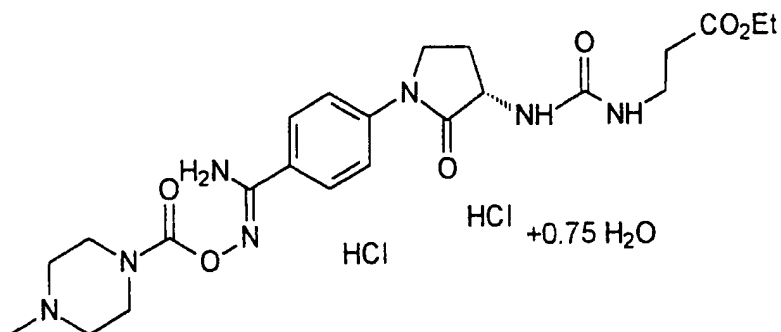
m. p. 131-136°C.

Analysis calculated for  $C_{23}H_{35}N_7O_6 \cdot 1.9 \text{ HCl}$ : C, 48.06; H, 6.47; N, 17.06.

Found: C, 48.09; H, 6.53; N, 17.29.

15 Example 3 (d)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny]carbonyl]oxy]amino]-methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester dihydrochloride



20

5 The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.  
m. p. 138-140°C (dec.).

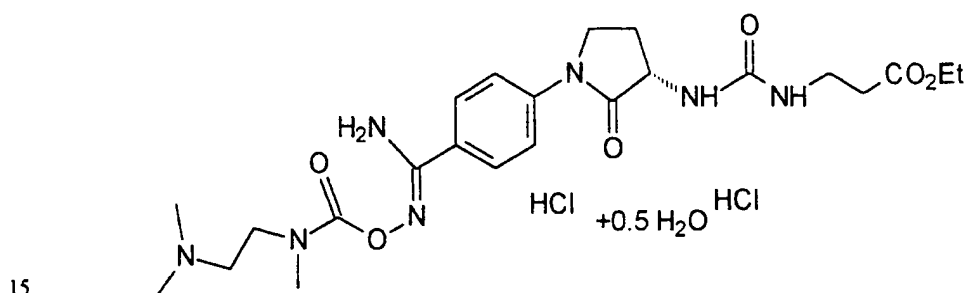
Analysis calculated for  $C_{23}H_{33}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.75 \text{ H}_2\text{O}$ :

C, 46.82; H, 6.24; N, 16.62.

10 Found: C, 46.91; H, 6.10; N, 16.68.

### Example 3 (e)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester dihydrochloride



The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.  
m. p. 134-138°C (dec)

20 Analysis calculated for  $C_{23}H_{35}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.66 \text{ H}_2\text{O}$ :

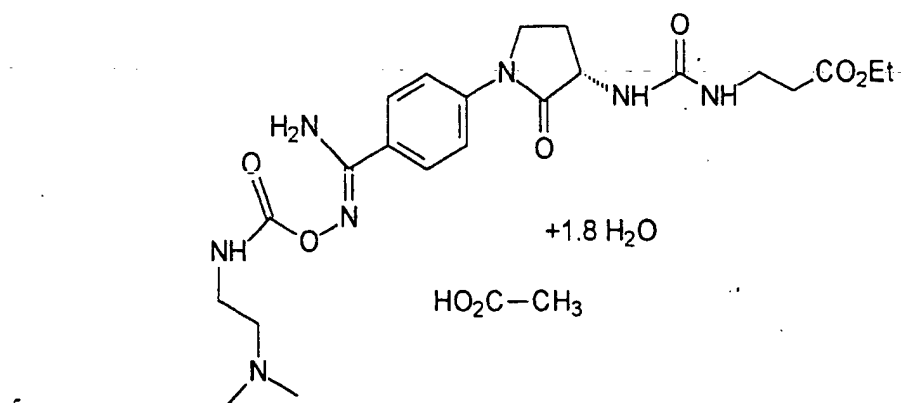
C, 47.02; H, 6.52; N, 16.69.

Found: C, 47.29; H, 6.87; N, 16.70.

### Example 3 (f)

25 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester monoacetate





The stripped down residue was taken up in dilute aqueous HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 155-160°C (dec.).

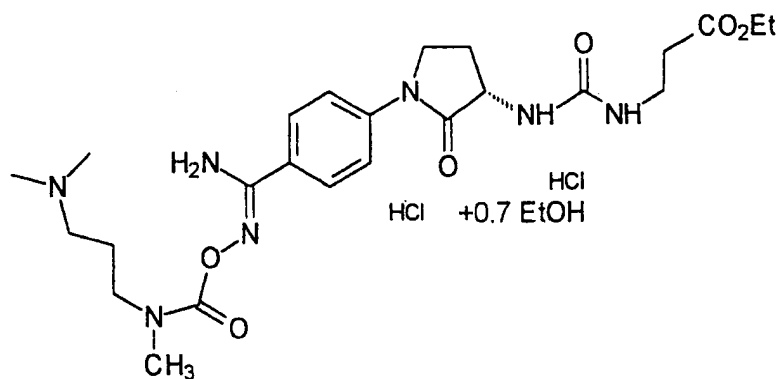
Analysis calculated for C<sub>22</sub>H<sub>33</sub>N<sub>7</sub>O<sub>6</sub>·1.0 HOAc·1.8 H<sub>2</sub>O:

10 C, 49.36; H, 7.01; N, 16.79.  
Found: C, 49.34; H, 7.12; N, 16.56.

### Example 3 (g)

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester dihydrochloride

15



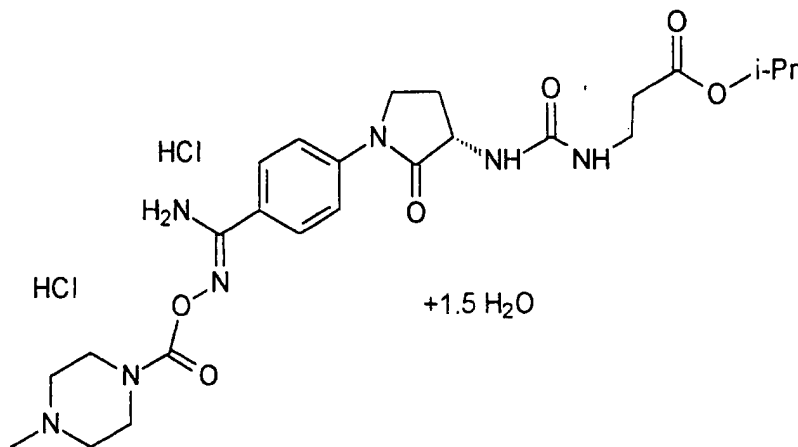
m. p. 130-133°C.

Analysis calculated for C<sub>24</sub>H<sub>37</sub>N<sub>7</sub>O<sub>6</sub>·2.0 HCl: C, 48.83; H, 6.97; N, 15.69.

Found: C, 49.00; H, 7.03; N, 15.60.

5 Example 3 (h)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
1-methylethyl ester dihydrochloride



10

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

135-136°C (dec.).

Analysis calculated for C<sub>24</sub>H<sub>35</sub>N<sub>7</sub>O<sub>6</sub>·2.0 HCl·1.5 H<sub>2</sub>O:

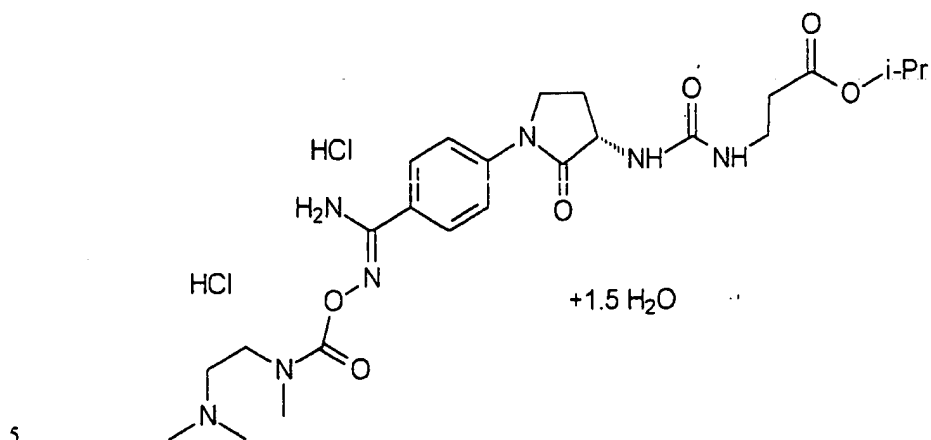
15

C, 46.68; H, 6.53; N, 15.88.

Found: C, 46.86; H, 6.44; N, 15.90.

Example 3 (i)

20 N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester dihydrochloride



The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 139-141°C (dec.).

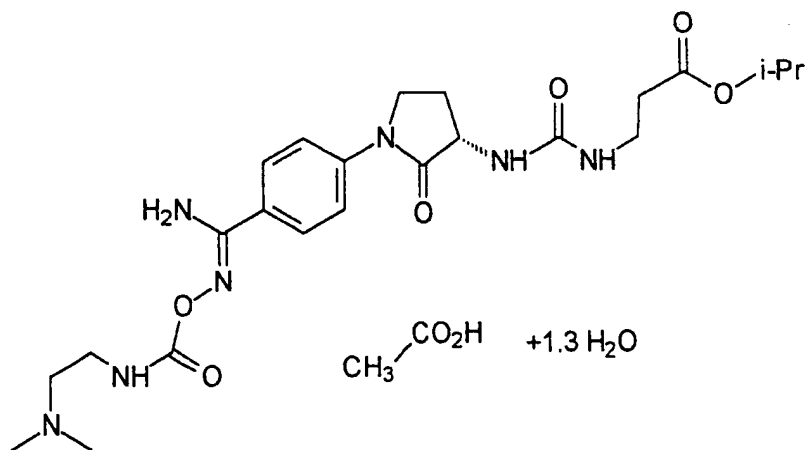
Analysis calculated for C<sub>24</sub>H<sub>37</sub>N<sub>7</sub>O<sub>6</sub>·2.0 HCl·1.5 H<sub>2</sub>O:

10 C, 46.53; H, 6.83; N, 15.83.

Found: C, 46.54; H, 6.63; N, 15.78.

### Example 3 (i)

15 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 1-methylethyl ester monoacetate



5           The ether precipitate was taken up in dilute HOAc and purified by  
RPHPLC using HOAc in the mobile phase.

m. p. 152-154°C (dec.).

Analysis calculated for  $C_{23}H_{35}N_7O_6 \cdot 1.0 \text{ HOAc} \cdot 1.3 \text{ H}_2\text{O}$ :

C, 50.98; H, 7.12; N, 16.65.

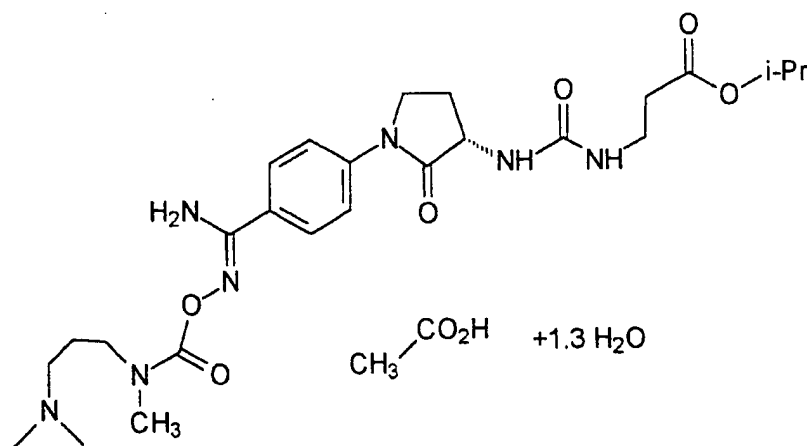
10

Found:       C, 50.92; H, 7.03; N, 17.01.

Example 3 (k)

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-  
2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester

15   monohydrate



m. p. 150-152°C (dec.).

Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 2.5 \text{ HCl} \cdot 1.0 \text{ H}_2\text{O}$ :

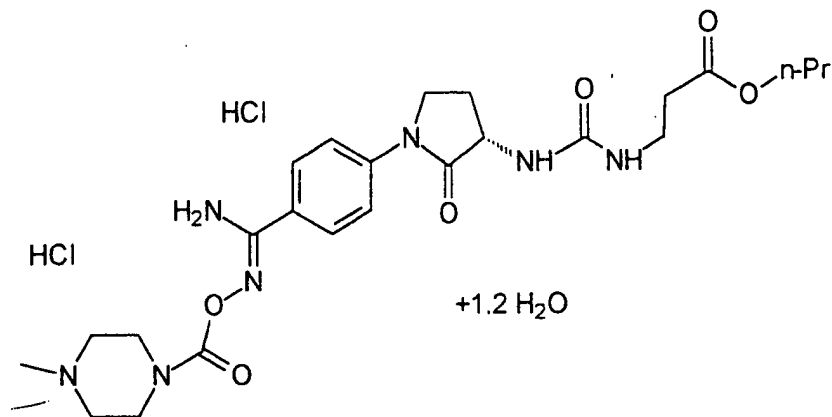
20

C, 49.52; H, 7.06; N, 16.17.

Found:       C, 49.57; H, 7.33; N, 16.17.

5 Example 3 (l)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester dihydrochloride



10

m. p. 158-160°C (dec.).

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

Analysis calculated for  $C_{24}H_{37}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.5 \text{ H}_2\text{O}$ :

15

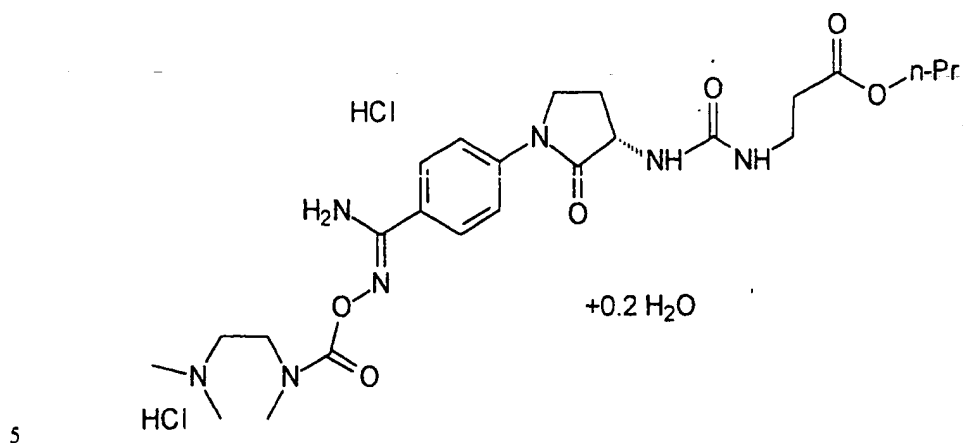
C, 48.08; H, 6.39; N, 16.35.

Found: C, 48.12; H, 6.67; N, 16.24.

Example 3 (m)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester dihydrochloride

20



The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 139-141°C (dec.).

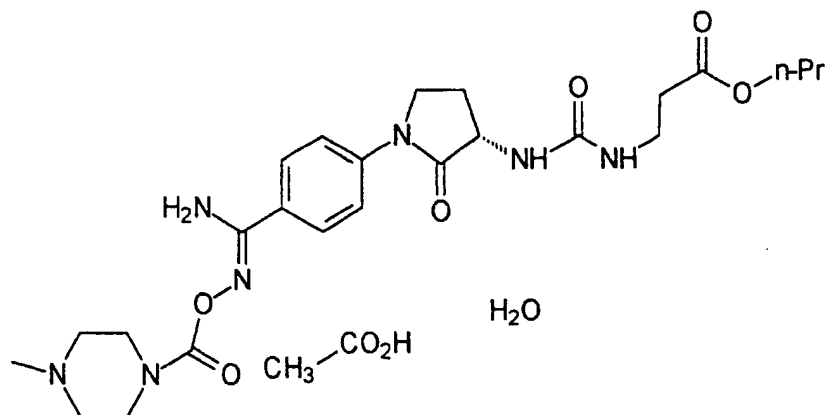
10 Analysis calculated for C<sub>24</sub>H<sub>37</sub>N<sub>7</sub>O<sub>6</sub>·2.0 HCl·0.2 H<sub>2</sub>O:

C, 48.36; H, 6.66; N, 16.45.

Found: C, 48.40; H, 6.74; N, 16.40.

### Example 3 (n)

15 N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine propyl ester monoacetate monohydrate



5 The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 156-157°C (dec.).

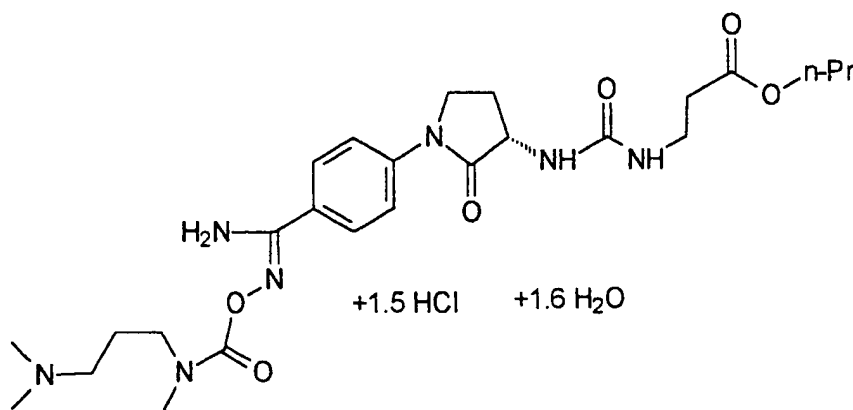
Analysis calculated for  $C_{23}H_{35}N_7O_6 \cdot 1.0 \text{ HOAc} \cdot 1.0 \text{ H}_2\text{O}$ :

C, 51.45; H, 7.08; N, 16.80.

10 Found: C, 51.53; H, 7.31; N, 17.01.

### Example 3 (o)

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester



m. p. 150-152°C (dec.).

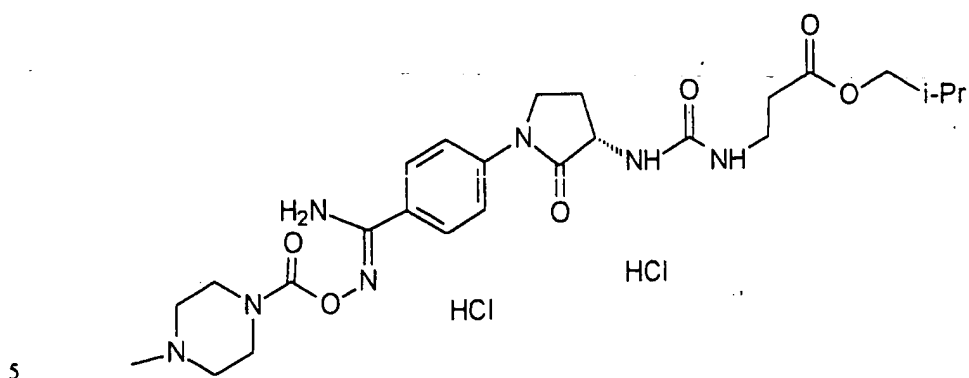
Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 1.5 \text{ HCl} \cdot 1.6 \text{ H}_2\text{O}$ :

C, 48.66; H, 7.14; N, 15.89.

20 Found: C, 48.62; H, 7.20; N, 15.79.

### Example 3 (p)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester  
25 dihydrochloride



m. p. 148.5-149.5°C (dec).

Analysis calculated for  $C_{25}H_{37}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.25 \text{ H}_2\text{O}$ :

C, 48.94; H, 6.57; N, 15.98.

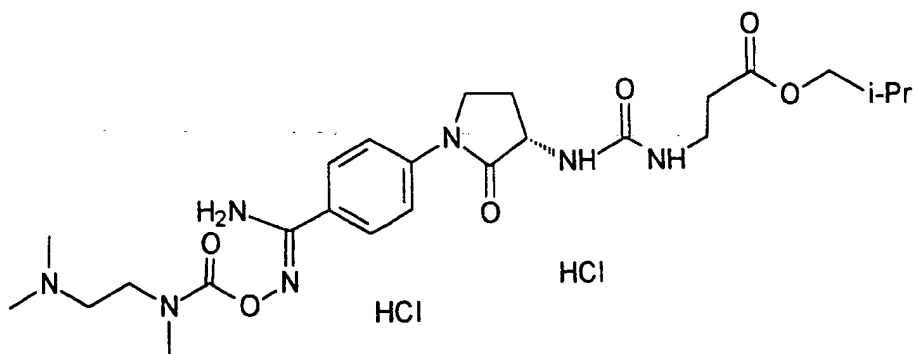
10

Found: C, 48.78; H, 6.41; N, 15.99.

### Example 3 (q)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 2-methylpropyl ester

15 dihydrochloride



m. p. 145-146°C (dec).

Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.25 \text{ H}_2\text{O}$ :

C, 49.14; H, 6.85; N, 16.05.

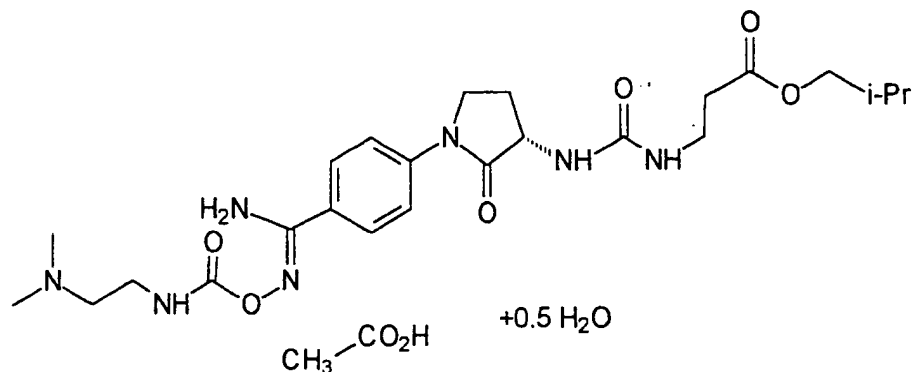
20

Found: C, 48.98; H, 6.60; N, 15.99.



5     Example 3 (r)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester monoacetate



10            The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 158-159°C (dec).

Analysis calculated for C<sub>24</sub>H<sub>37</sub>N<sub>7</sub>O<sub>6</sub> · 1.0 HOAc · 0.25 H<sub>2</sub>O:

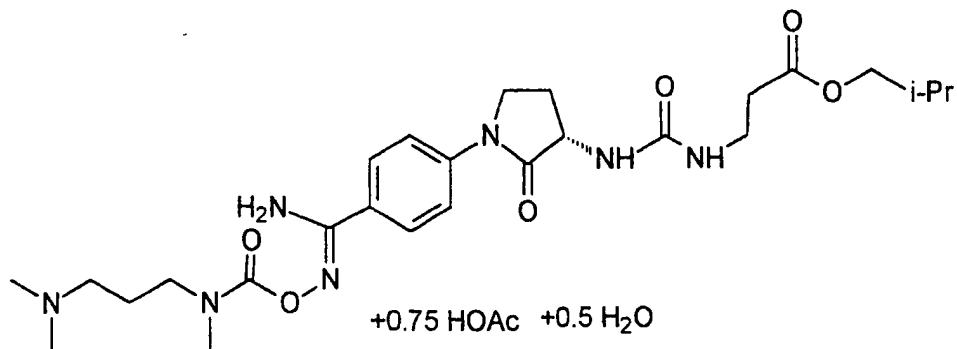
C, 53.05; H, 7.17; N, 16.66.

15

Found:        C, 53.02; H, 7.32; N, 16.78.

Example 3 (s)

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester



20            The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

5 m.p. 131.5-133°C.

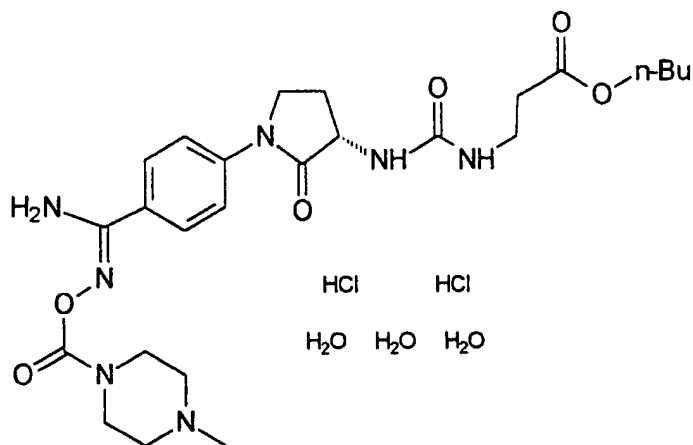
Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 0.75 \text{ HOAc} \cdot 0.5 \text{ H}_2\text{O}$ :

C, 54.89; H, 7.54; N, 16.29.

Found: C, 54.57; H, 7.45; N, 16.62.

10 Example 3 (t)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine butyl ester dihydrochloride



15

m. p. 115-117°C (dec.).

Analysis calculated for  $C_{25}H_{37}N_7O_6 \cdot 2.2 \text{ HCl} \cdot 3.0 \text{ H}_2\text{O}$ :

C, 45.10; H, 6.84; N, 14.72.

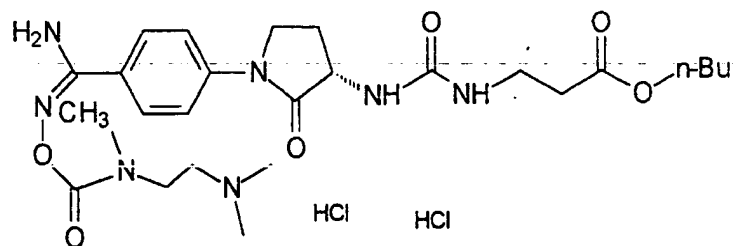
Found: C, 45.08; H, 6.69; N, 14.75.

20

Example 3 (u)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine butyl ester dihydrochloride

5



m. p. 144-146°C (dec.).

Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 2.0 \text{ HCl}$ :

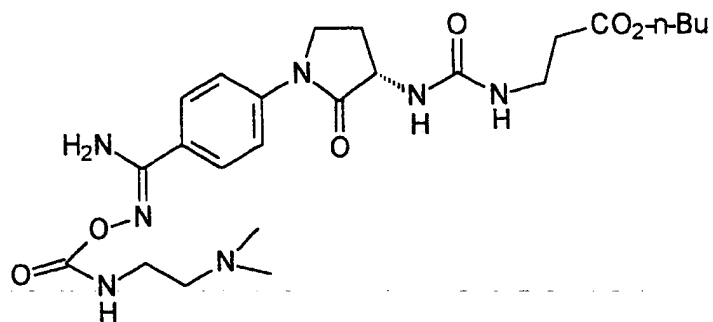
C, 49.51; H, 6.81; N, 16.16.

10

Found: C, 49.61; H, 7.31; N, 16.18.

### Example 3 (v)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine butyl ester dihydrochloride



15

Analysis calculated for  $C_{24}H_{37}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 0.8 \text{ H}_2\text{O}$ :

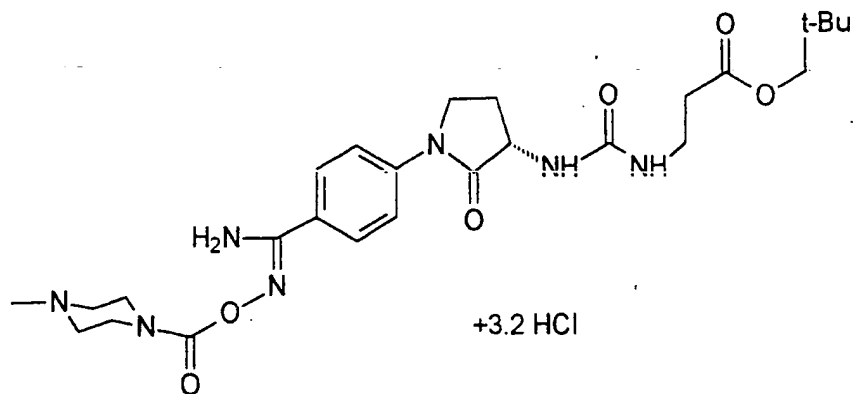
C, 47.50; H, 6.74; N, 16.15.

Found: C, 47.52; H, 6.56; N, 16.62.

20

### Example 3 (w)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny]carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester



5

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 166-167°C (dec.).

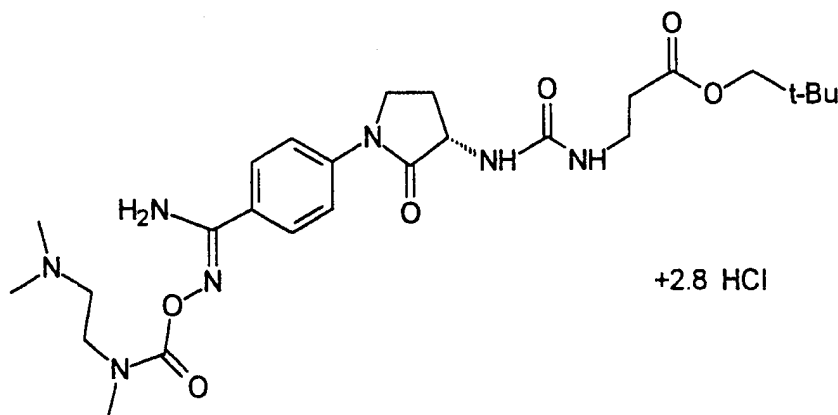
10 Analysis calculated for  $C_{26}H_{39}N_7O_6 \cdot 3.2 \text{ HCl}$ :

C, 47.15; H, 6.42; N, 14.80.

Found: C, 47.20; H, 6.13; N, 14.47.

### Example 3 (x)

15 N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester



5 The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 130-135°C and 140°C (dec.)

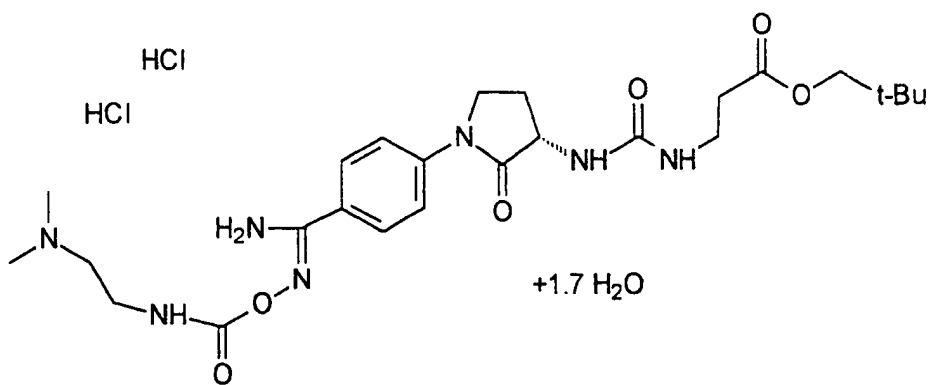
Analysis calculated for  $C_{26}H_{41}N_7O_6 \cdot 2.8 HCl$ : C, 48.06; H, 6.79; N, 15.09.

Found: C, 47.82; H, 6.69; N, 15.09.

10

### Example 3 (y)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester dihydrochloride



15

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 122-126°C and 170-190°C (dec.)

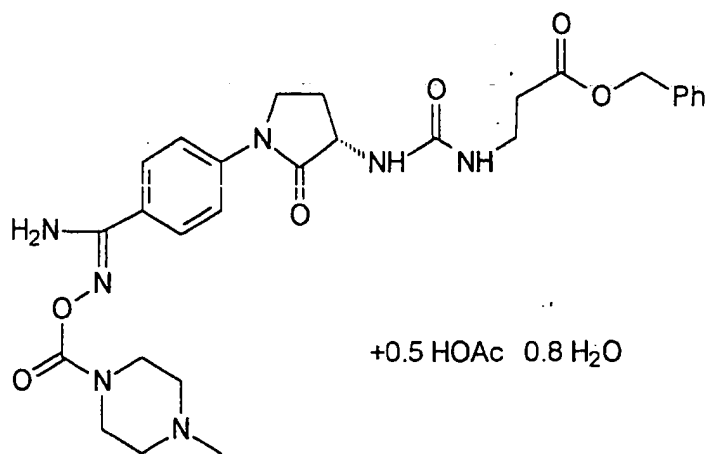
20 Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 2.0 HCl \cdot 1.7 H_2O$ :

C, 47.13; H, 7.02; N, 15.39.

Found: C, 47.17; H, 6.63; N, 15.34.

### Example 3 (z)

25 N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny]carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine phenylmethyl ester



5

The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 154-158°C (dec.).

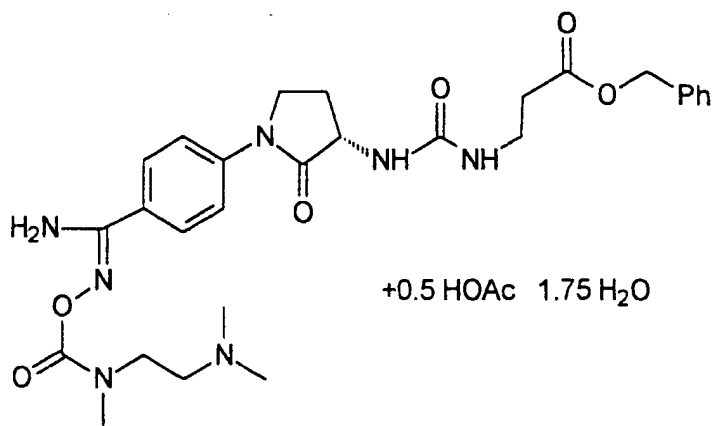
10 Analysis calculated for C<sub>28</sub>H<sub>35</sub>N<sub>7</sub>O<sub>6</sub> · 0.5 HOAc · 0.8 H<sub>2</sub>O:

C, 57.10; H, 6.38; N, 16.07.

Found: C, 57.04; H, 6.08; N, 15.99.

### Example 3 (aa)

15 N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester



5 The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 68-70°C.

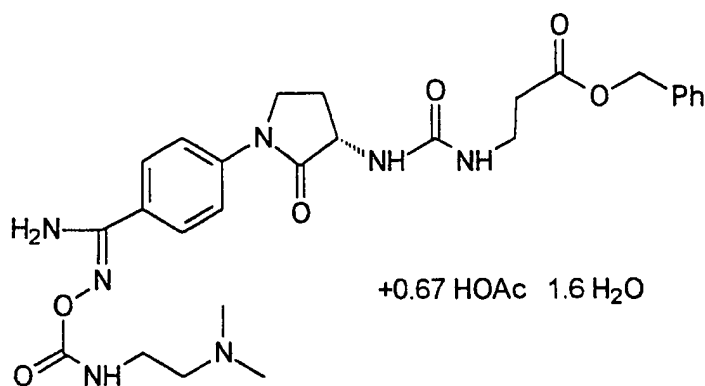
Analysis calculated for  $C_{28}H_{37}N_7O_6 \cdot 0.5 \text{ HOAc} \cdot 1.75 \text{ H}_2\text{O}$ :

C, 55.34; H, 6.32; N, 16.13.

10 Found: C, 55.44; H, 6.51; N, 15.40.

### Example 3 (bb)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine phenylmethyl ester



15

The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 159-161°C (dec.).

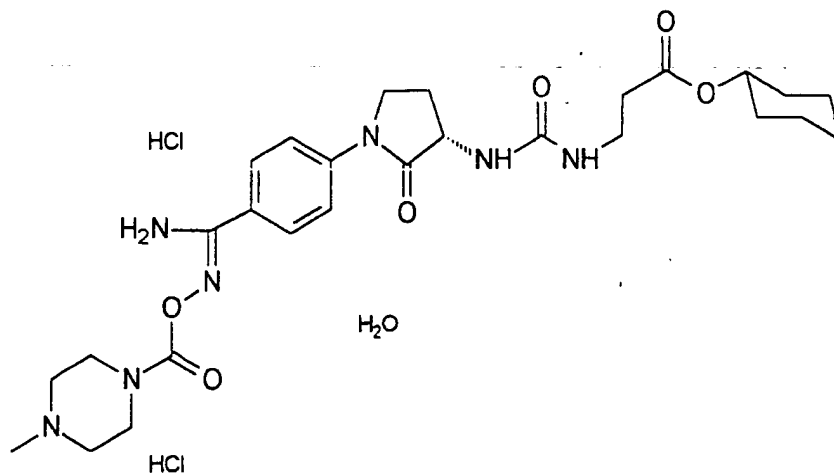
20 Analysis calculated for  $C_{27}H_{35}N_7O_6 \cdot 0.67 \text{ HOAc} \cdot 1.60 \text{ H}_2\text{O}$ :

C, 54.68; H, 6.62; N, 15.76.

Found: C, 54.44; H, 6.13; N, 15.72.

### Example 3 (cc)

25 N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine cyclohexyl ester dihydrochloride monohydrate



The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 137-139°C (dec.).

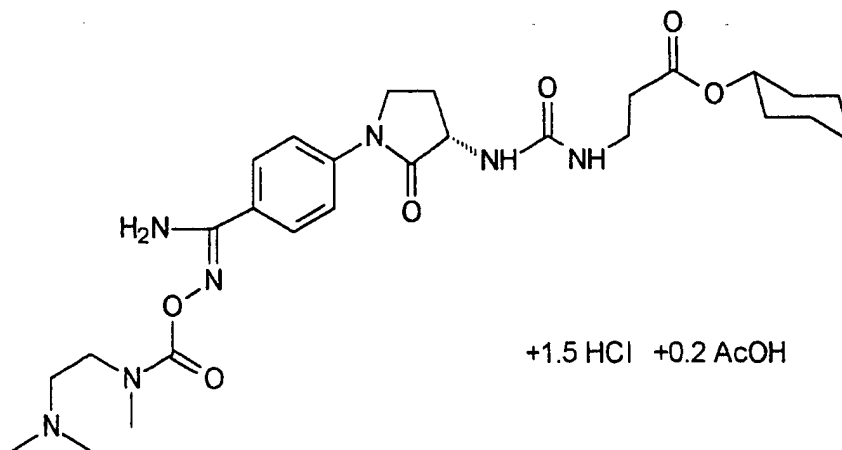
Analysis calculated for  $C_{24}H_{35}N_7O_6 \cdot 2.0 \text{ HCl} \cdot 1.2 \text{ H}_2\text{O}$ :

10 C, 47.09; H, 6.49; N, 16.02.  
Found: C, 47.00; H, 6.15; N, 15.99.

### Example 3 (dd)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester

15





5           The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 135-137°C (dec.).

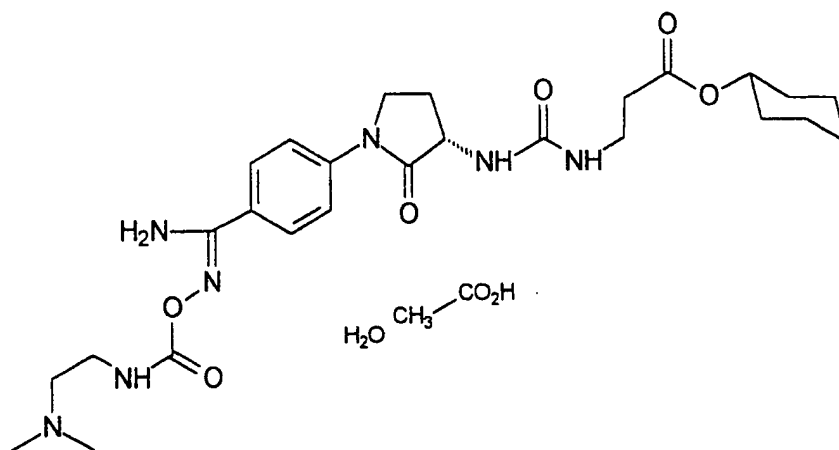
Analysis calculated for  $C_{27}H_{41}N_7O_6 \cdot 1.6 \text{ HCl}$ : C, 52.47; H, 6.95; N, 15.87.

Found: C, 52.51; H, 7.08; N, 15.62.

10

Example 3 (ee)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine cyclohexyl ester monoacetate monohydrate



The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 157-158°C (dec.).

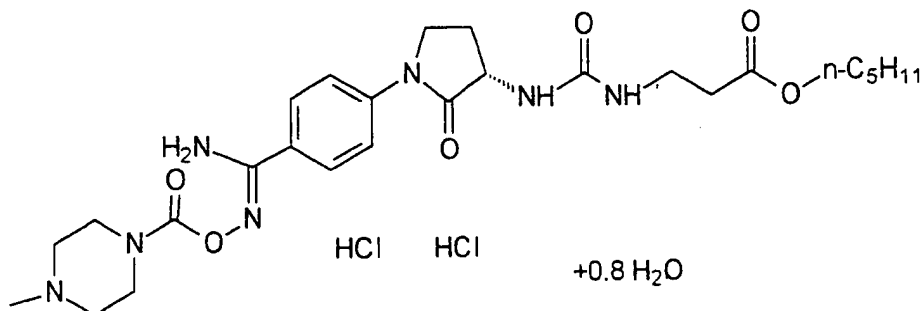
20   Analysis calculated for  $C_{26}H_{39}N_7O_6 \cdot 1.0 \text{ HOAc} \cdot 1.0 \text{ H}_2\text{O}$ :

C, 53.92; H, 7.27; N, 15.72.

Found: C, 53.84; H, 7.13; N, 15.78.

5 Example 3 (ff)

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino)methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine pentyl ester dihydrochloride



10

The ether precipitate was taken up in dilute HCl and purified by RPHPLC using HCl in the mobile phase.

m. p. 165-167°C (dec.).

Analysis calculated for C<sub>26</sub>H<sub>39</sub>N<sub>7</sub>O<sub>6</sub> · 2.0 HCl · 1.0 H<sub>2</sub>O:

15

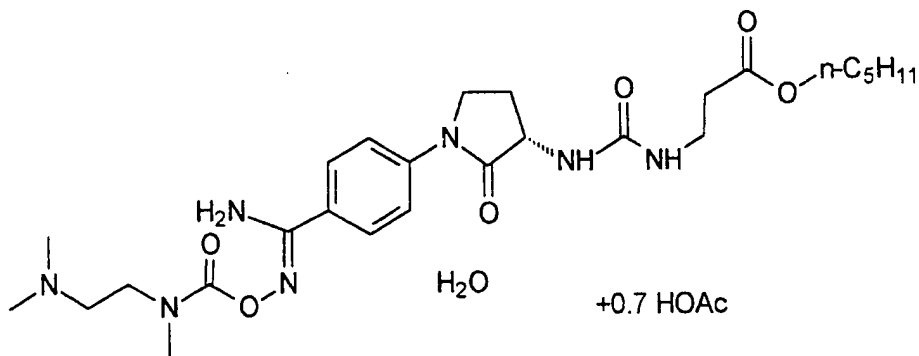
C, 49.06; H, 6.81; N, 15.40.

Found: C, 49.46; H, 6.50; N, 15.34.

Example 3 (gg)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine pentyl ester monohydrate

20



5 The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 126-127°C (dec.).

Analysis calculated for  $C_{26}H_{41}N_7O_6 \cdot 0.7 \text{ HOAc} \cdot 1.0 \text{ H}_2\text{O}$ :

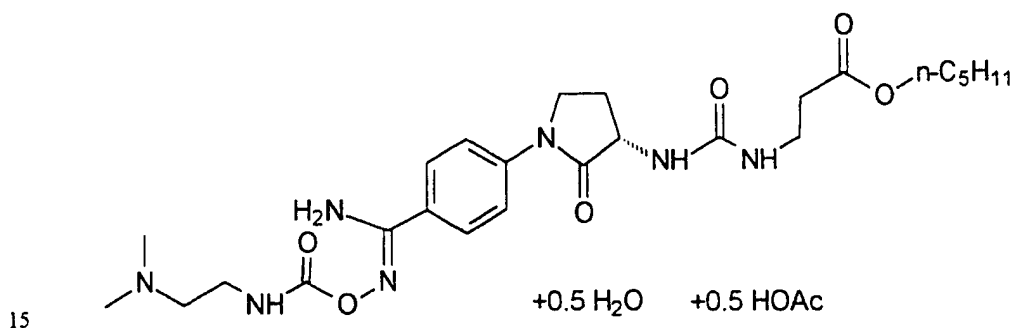
C, 54.22; H, 7.60; N, 16.21.

10

Found: C, 53.98; H, 7.46; N, 16.60.

### Example 3 (hh)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine pentyl ester



The ether precipitate was taken up in dilute HOAc and purified by RPHPLC using HOAc in the mobile phase.

m. p. 159-160°C (dec.).

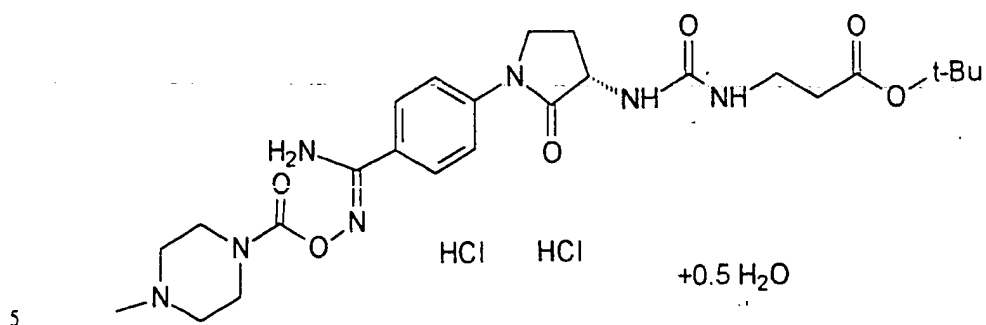
20 Analysis calculated for  $C_{25}H_{39}N_7O_6 \cdot 0.5 \text{ HOAc} \cdot 0.5 \text{ H}_2\text{O}$ :

C, 54.53; H, 7.39; N, 17.12.

Found: C, 54.41; H, 7.25; N, 17.46.

### Example 3 (ii)

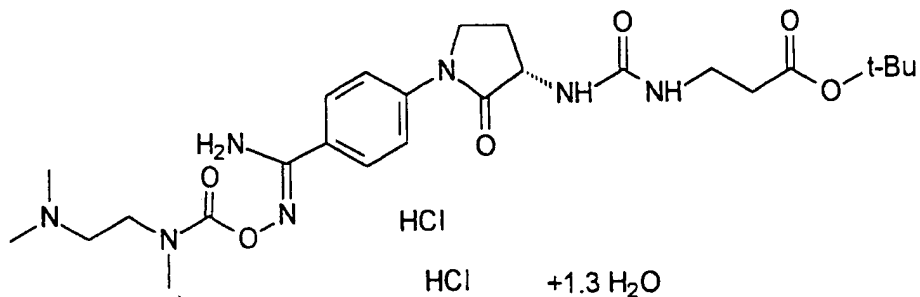
25 N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny]carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester dihydrochloride



<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 1.39 (s, 9H), 1.88 (m, 1H), 2.32 (t, J = 7 Hz, 2H), 2.37-2.44 (m, 1H), 2.75 (d, J = 5 Hz, 3H), 3.01 (m, 2H), 3.18 (t, J = 7 Hz, 2H), 3.23-3.41 (m, 4H), 3.70-3.80 (m, 2H), 4.41 (m, 1H) 6.16 (br. s, 1H), 6.50 (br.s, 1H),  
10 6.77 (br.s, 2H), 7.71 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H).

### Example 3 (ii)

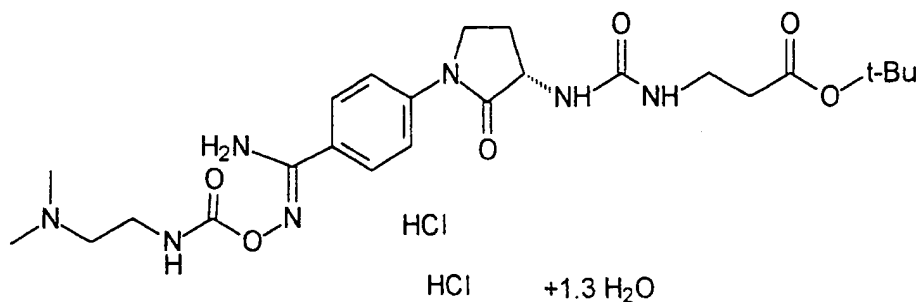
N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester  
15 dihydrochloride



<sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 1.40 (s, 9H), 1.89 (m, 1H), 2.32 (t, J = 7 Hz, 2H), 2.35-2.44 (m, 1H), 2.79 (d, J = 5 Hz, 6H), 2.96 (br. s, 3H), 3.18 (t, J = 7 Hz, 2H), 3.24 (m, 3H), 3.73-3.82 (m, 3H), 4.41 (m, 1H) 6.12 (br. s, 1H), 6.50 (br.s, 1H),  
20 6.89 (br.s, 2H), 7.73 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H).

5 Example 3 (kk)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1dimethylethyl ester



10

<sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO) δ 1.42 (s, 9H), 2.18 (m, 6H), 2.34 (t, J = 7 Hz, 2H), 2.38 (t, J = 7 Hz, 2H), 2.40-2.47 (m, 1H), 3.20 (d, J = 7 Hz, 2H), 3.25 (d, J = 7 Hz, 2H), 3.74-3.82 (m, 2H), 4.38-4.48 (m, 1H), 6.14 (t, J = 7 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 6.77 (br.s, 2H), 7.24 (t, J = 7 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.82 (d, J =

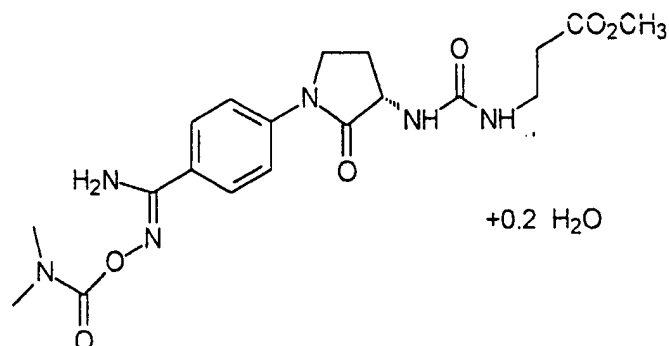
15

7 Hz, 2H).

5

Example 4

Preparation of N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester



To a stirred suspension of the product of Example 1(a) (504 mg, 1.4 mmol) in pyridine (5 mL) was added dropwise dimethylcarbamoyl chloride (149 mg, 1.4 mmol). After 1 hour, the crude product was precipitated with diethyl ether, washed with water and dried affording the product (524 mg, 86% yield) [m. p. 189-192°C (dec.)].

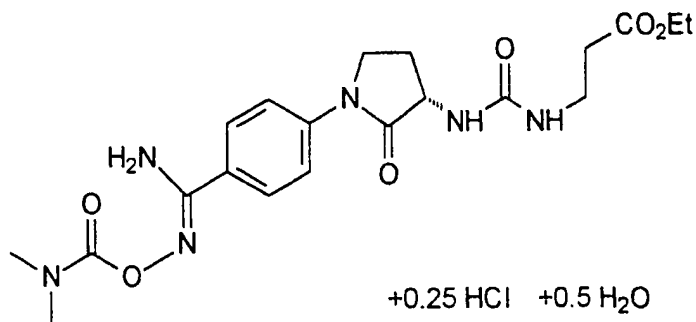
Analysis calculated for C<sub>19</sub>H<sub>26</sub>N<sub>6</sub>O<sub>6</sub> · 0.2 H<sub>2</sub>O: C, 52.10; H, 6.07; N, 19.18.

15 Found: C, 52.00; H, 6.20; N, 18.94.

The following compounds were prepared analogously:

Example 4 (a)

20 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester



5 The product was purified by RPHPLC using HCl in the mobile phase.

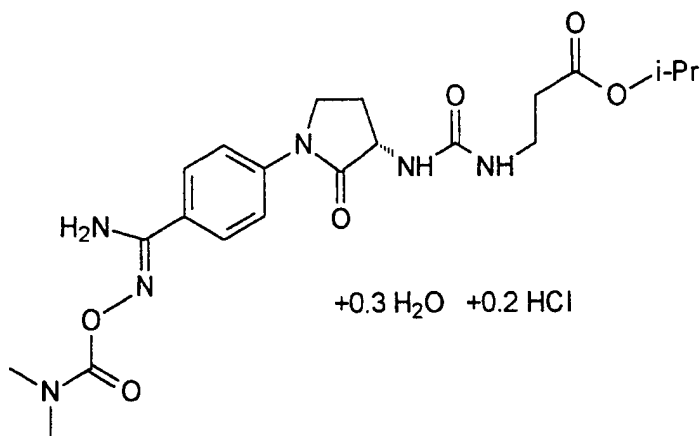
m. p. 174°C (dec.).

Analysis calculated for  $C_{20}H_{28}N_6O_6 \cdot 0.9 H_2O$ : C, 51.69; H, 6.46; N, 18.09.

Found: C, 51.71; H, 6.30; N, 17.94.

10 Example 4 (b)

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine 1-methylethyl ester



15 The product was purified by RPHPLC using HCl in the mobile phase.

m. p. 174-176°C (dec.).

Analysis calculated for  $C_{21}H_{30}N_6O_6 \cdot 0.2 HCl \cdot 0.3 H_2O$ :

C, 53.08; H, 6.53; N, 17.69.

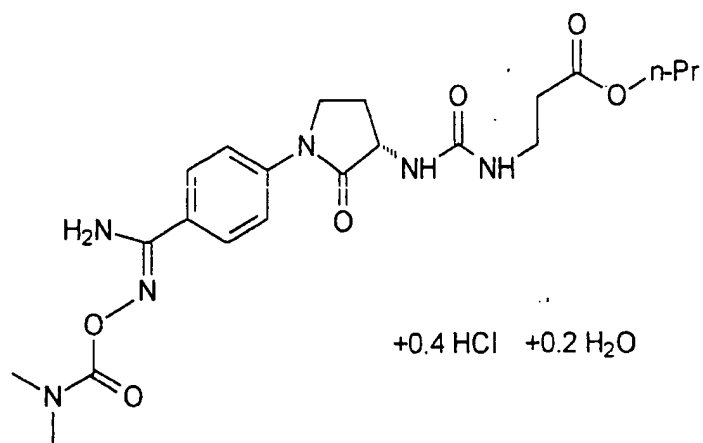
Found: C, 52.99; H, 6.73; N, 17.63.

20

Example 4 (c)

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine propyl ester

5



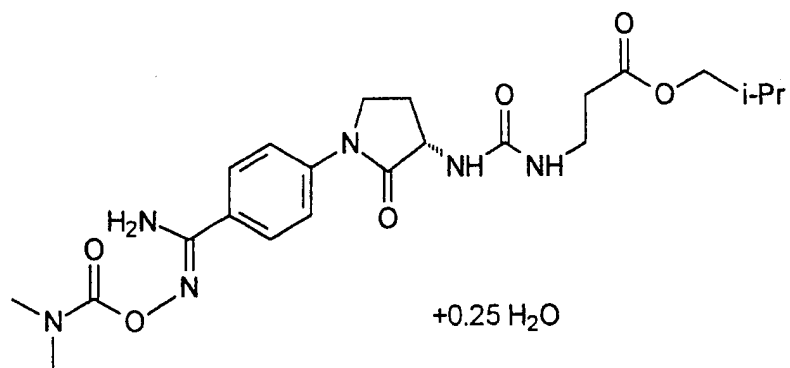
The product was purified by RPHPLC using HCl in the mobile phase.  
m. p. 170-175°C (dec.).

Analysis calculated for C<sub>21</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub> · 0.4 HCl · 0.2 H<sub>2</sub>O:

10 C, 52.49; H, 6.46; N, 17.48.  
Found: C, 52.66; H, 6.41; N, 17.34.

#### Example 4 (d)

15 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester



The product was purified by RPHPLC using HCl in the mobile phase.  
m. p. 167-168°C (dec.).



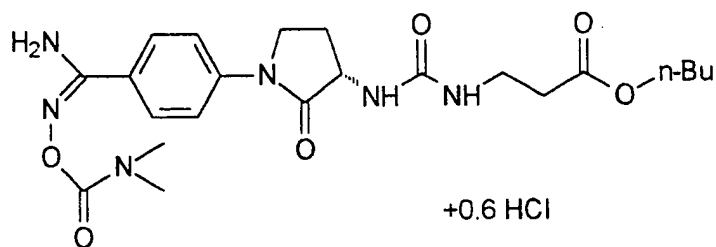
5 Analysis calculated for  $C_{22}H_{33}N_6O_6 \cdot 0.25 H_2O$ : C, 54.93; H, 6.81; N, 17.47.

Found: C, 54.71; H, 6.81; N, 17.46.

Example 4 (e)

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-

10 oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine butyl ester,



m. p. 176-177°C.

Analysis calculated for  $C_{22}H_{32}N_6O_6 \cdot 0.6 HCl$ : C, 53.02; H, 6.59; N, 16.86.

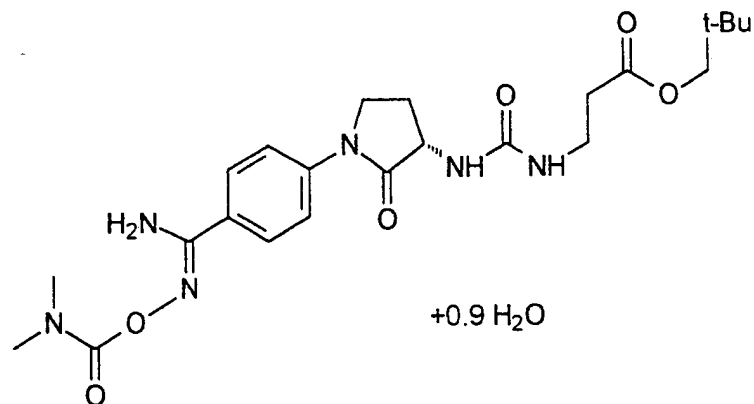
15

Found: C, 53.12; H, 6.58; N, 17.05.

Example 4 (f)

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-

oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2,2-methylpropyl ester



20

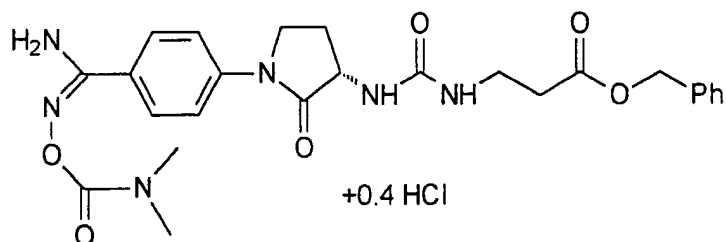
5 m. p. 177-182°C (dec.)

Analysis calculated for  $C_{23}H_{34}N_6O_6 \cdot 0.9 H_2O$ : C, 54.51; H, 7.12; N, 16.58.

Found: C, 54.29; H, 6.72; N, 16.37.

Example 4 (g)

10 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester



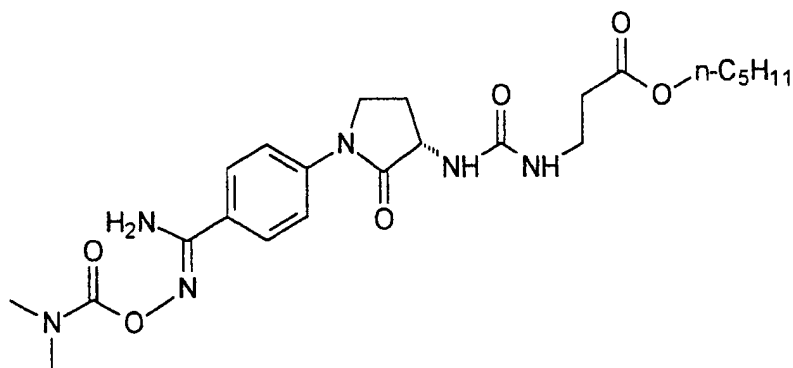
m. p. 179-180°C.

15 Analysis calculated for  $C_{25}H_{30}N_6O_6 \cdot 0.8 H_2O$ : C, 57.20; H, 6.07; N, 16.01.

Found: C, 57.10; H, 5.76; N, 15.66.

Example 4 (h)

20 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester



The product was purified by RPHPLC using HCl in the mobile phase.

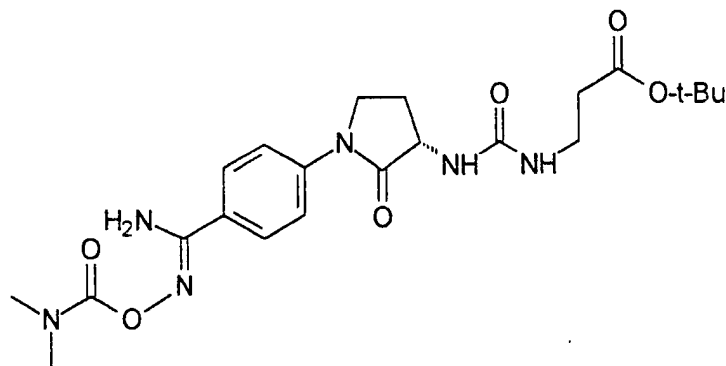
5 m. p. 177-179°C (dec.).

Analysis calculated for  $C_{23}H_{34}N_6O_6$ : C, 56.31; H, 6.99; N, 17.13.

Found: C, 56.29; H, 7.40; N, 17.03.

Example 4 (i)

10 N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyloxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester

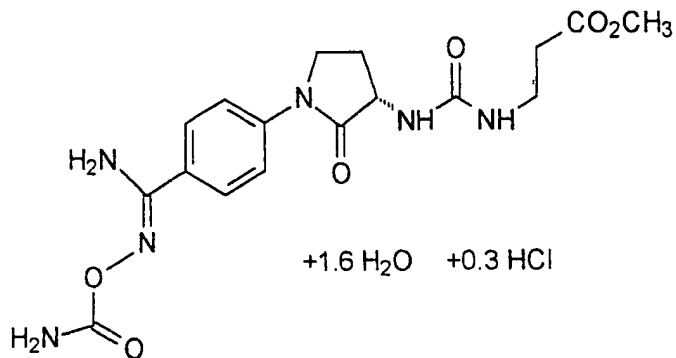


15  $^1\text{H-NMR}$  ( $d_6$ -DMSO)  $\delta$  1.39 (s, 9H), 1.89 (m, 1H), 2.33 (t,  $J = 7$  Hz, 2H), 2.34 (m, 1H), 2.72 (br. s, 6H), 3.19 (t,  $J = 7$  Hz, 2H), 3.70-3.82 (m, 2H), 3.38-4.48 (m, 1H), 6.15 (br. s, 1H), 6.50 (br. s, 1H), 7.28 (br. s, 2H), 7.73 (d,  $J = 9$  Hz, 2H), 7.78 (d,  $J = 9$  Hz, 2H).

5

Example 5

Preparation of N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]-phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine methyl ester



10

To a solution of the product of Example 1(a) (560 mg, 1.5 mmol) in water (5 mL) was added 3M HCl (0.5 mL) followed by potassium cyanate (125 mg, 1.5 mmol). After stirring for 2 hours, the precipitate was filtered. The product was redissolved in dilute HCl and purified by RPHPLC using HCl in the mobile phase affording the product as a lyophilized powder (560 mg, 75% yield) [177-178°C (dec.)].

15

Analysis calculated for C<sub>17</sub>H<sub>22</sub>N<sub>6</sub>O<sub>6</sub> · 0.3 HCl · 1.6 H<sub>2</sub>O:

C, 45.77; H, 5.76; N, 18.84.

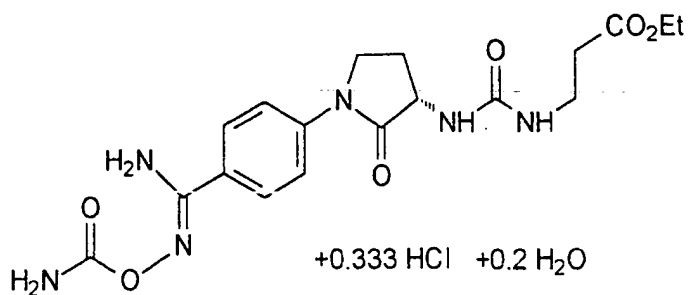
Found: C, 45.81; H, 5.36; N, 18.62.

20

The following compounds were prepared analogously:

Example 5 (a)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine ethyl ester



m. p. 176-177°C (dec.).

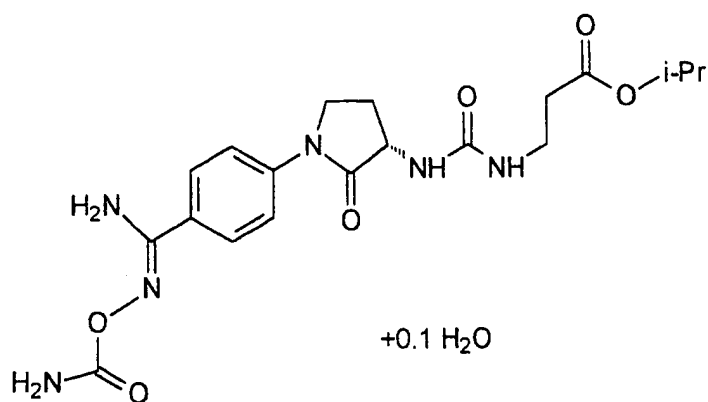
Analysis calculated for C<sub>18</sub>H<sub>24</sub>N<sub>6</sub>O<sub>6</sub>·0.33 HCl ·0.2 H<sub>2</sub>O:

C, 49.58; H, 5.72; N, 19.27.

Found: C, 49.77; H, 5.73; N, 19.19.

### Example 5 (b)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester



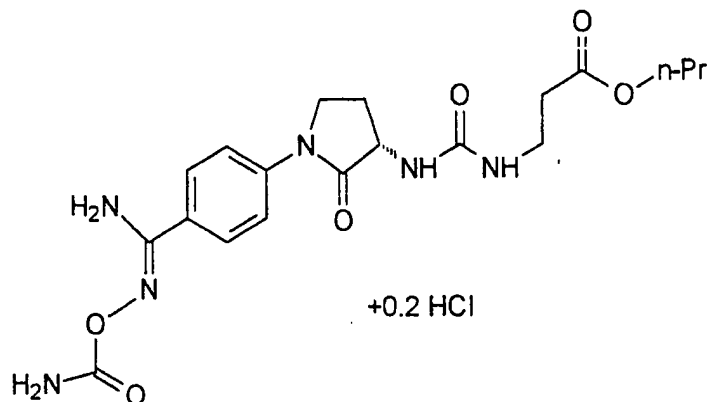
m. p. 169-172°C (dec.).

Analysis calculated for C<sub>19</sub>H<sub>26</sub>N<sub>6</sub>O<sub>6</sub>·0.1 HCl: C, 52.09; H, 6.00; N, 19.18.

Found: C, 52.08; H, 6.24; N, 18.87.

5 Example 5 (c)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester



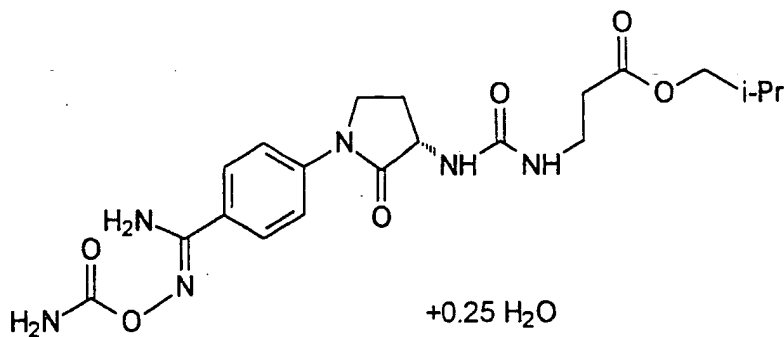
10 m. p. 174-176°C (dec.).

Analysis calculated for  $C_{19}H_{26}N_6O_6 \cdot 0.2 \text{ HCl}$ : C, 51.66; H, 5.98; N, 19.02.

Found: C, 51.70; H, 5.74; N, 18.90.

Example 5 (d)

15 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester



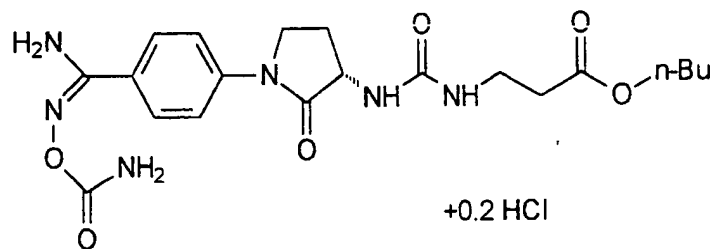
m. p. 168-169°C (dec.).

Analysis calculated for  $C_{20}H_{28}N_6O_6 \cdot 0.25 \text{ H}_2\text{O}$ : C, 53.03; H, 6.34; N, 18.55.

Found: C, 53.13; H, 6.42; N, 18.61.

5 Example 5 (e)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester



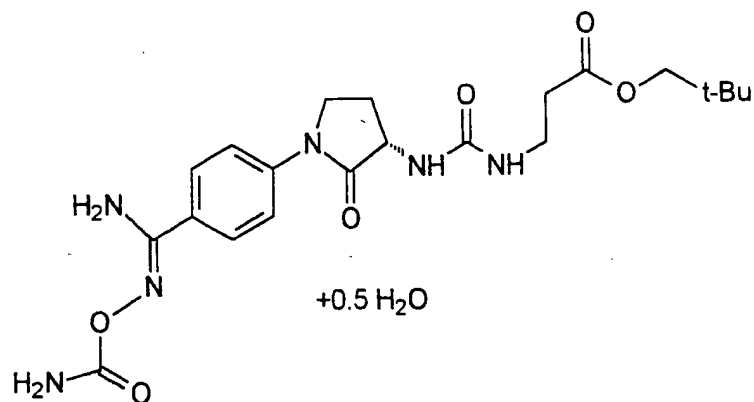
m. p. 184-186°C.

10 Analysis calculated for  $C_{20}H_{28}N_6O_6 \cdot 0.2 \text{ HCl}$ : C, 52.71; H, 6.24; N, 18.44.  
 Found: C, 52.71; H, 6.32; N, 18.24.

Example 5 (f)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester

15



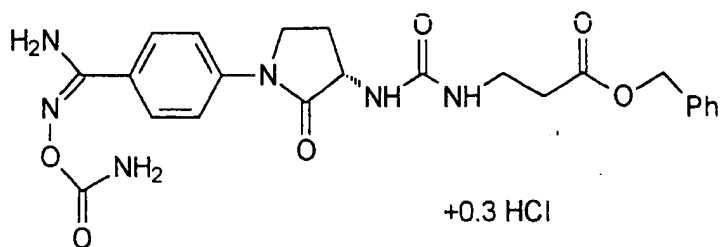
The reaction was carried out as described above except THF:water (5:1) was used as the solvent.

20 m. p. 169-173°C.

Analysis calculated for  $C_{21}H_{30}N_6O_6 \cdot 0.5 \text{ H}_2\text{O}$ : C, 53.49; H, 6.63; N, 17.82.  
 Found: C, 53.46; H, 6.28; N, 17.72.

5 Example 5 (g)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester



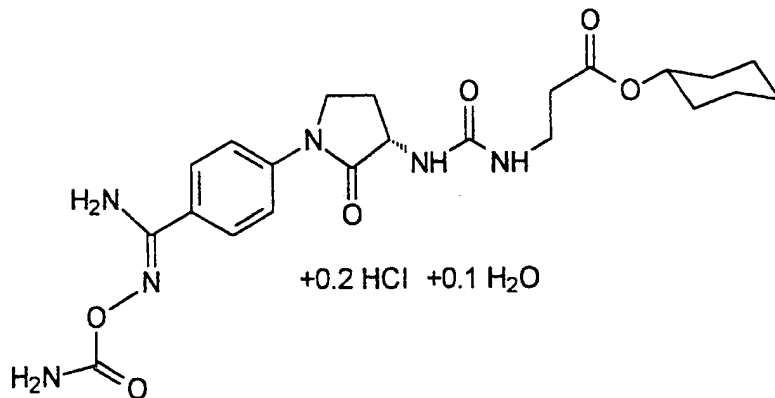
10 m. p. 174-176°C.

Analysis calculated for  $C_{23}H_{26}N_6O_6 \cdot 1.0 \text{ HCl}$ : C, 55.99; H, 5.37; N, 17.03.

Found: C, 56.03; H, 5.39; N, 16.99.

Example 5 (h)

15 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester



m. p. 167-168°C (dec.).

20 Analysis calculated for  $C_{22}H_{30}N_6O_6 \cdot 0.2 \text{ HCl} \cdot 0.1 \text{ H}_2\text{O}$ :

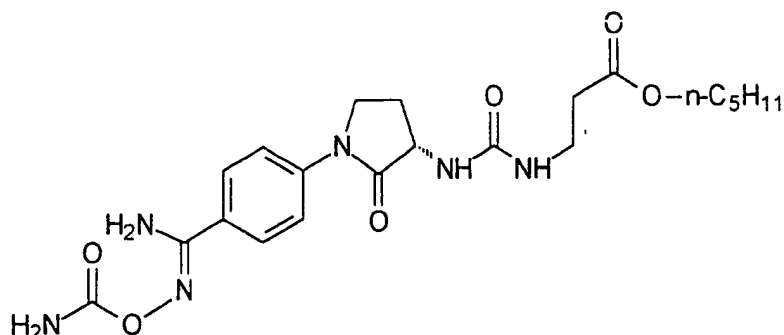
C, 54.64; H, 6.34; N, 17.38.

Found: C, 54.67; H, 6.06; N, 17.20.



5 Example 5 (i)

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester



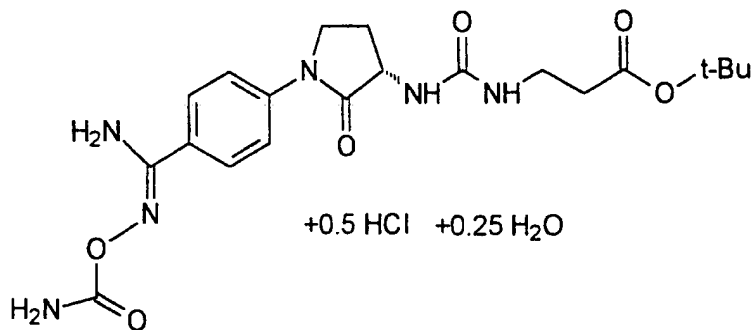
10 m. p. 170.5-172°C (dec.).

Analysis calculated for  $C_{21}H_{30}N_6O_6$ : C, 54.01; H, 6.58; N, 18.00.

Found: C, 54.19; H, 6.45; N, 18.01.

Example 5 (j)

15 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester

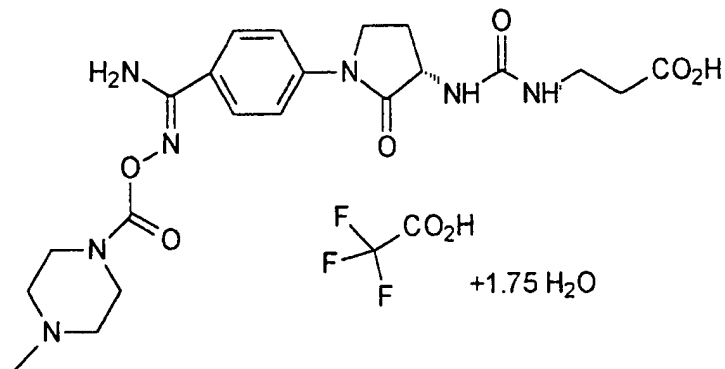


20 <sup>1</sup>H-NMR (*d*<sub>6</sub>-DMSO) δ 1.39 (s, 9H), 1.88 (m, 1H), 2.33 (t, J = 7 Hz, 2H), 2.34-2.46 (m, 1H), 3.19 (q, J = 7Hz, 2H), 3.72-3.80 (m, 2H), 4.40 (m, 1H), 6.13 (t, J = 7 Hz, 1H), 6.46 (d, J = 7 Hz, 1H), 6.67 (br. s, 2H), 6.85 (br.s, 2H), 7.73 (d, J = 9 Hz, 2H), 7.82 (d, J=9Hz, 2H).

5

Example 6

Preparation of N-[[[(3S)-1-[4-[Imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]-amino]methyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine mono(trifluoroacetate)



10

The product of Example 3 (ii) (660 mg, 1.24 mmol) was dissolved in trifluoroacetic acid:water (10 mL) (9:1). After stirring for 2 hours, the reaction mixture was concentrated and the residue purified on RPHPLC using TFA in the mobile phase affording the product as a lyophilized powder (308 mg, 55% yield) [m. p. 110-114°C (dec.)].

15

Analysis calculated for  $C_{21}H_{29}N_7O_6 \cdot 1.0 \text{ TFA} \cdot 1.75 \text{ H}_2\text{O}$ :

C, 44.48; H, 5.44; N, 15.79.

Found: C, 44.20; H, 5.22; N, 15.82.

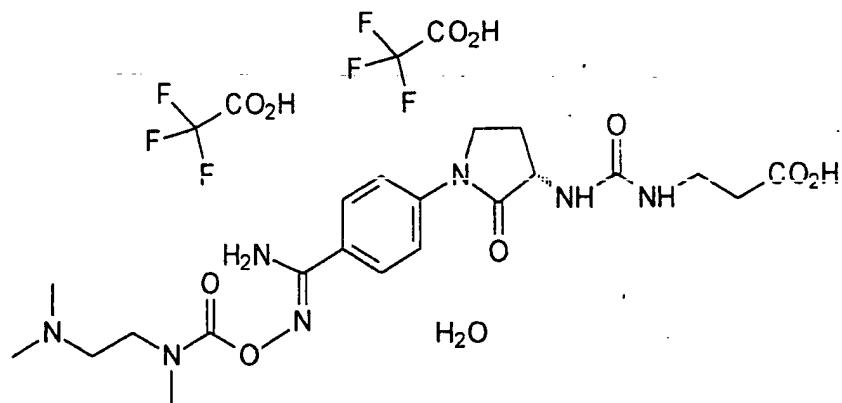
20

The following compounds were prepared analogously from the products of Examples 3(jj), 3(kk), 4(i) and 5(j) respectively:

Example 6 (a)

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine bis(trifluoroacetate) monohydrate

25



5

$^1\text{H-NMR}$  ( $d_6$ -DMSO)  $\delta$  1.89 (m, 1H), 2.35 (t,  $J=7$  Hz, 2H), 2.37-2.46 (m, 1H), 2.83 (d,  $J=5$  Hz, 6H), 2.95 (br. s, 3H), 3.20 (br. t,  $J=7$  Hz, 2H), 3.26 (d,  $J=6$  Hz, 2H), 3.55-3.60 (m, 2H), 3.61-3.70 (m, 2H), 4.41 (br. t,  $J=7$  Hz, 1H), 6.17 (br. s, 1H), 6.47 (d,  $J=8$  Hz, 1H), 6.63 (s, 2H), 7.73 (d,  $J=8$  Hz, 2H), 7.75 (d,  $J=8$  Hz, 2H), 9.42 (br. s, 1H).

Analysis calculated for  $\text{C}_{21}\text{H}_{31}\text{N}_7\text{O}_6 \cdot 2.0 \text{ TFA} \cdot 1.0 \text{ H}_2\text{O}$ :

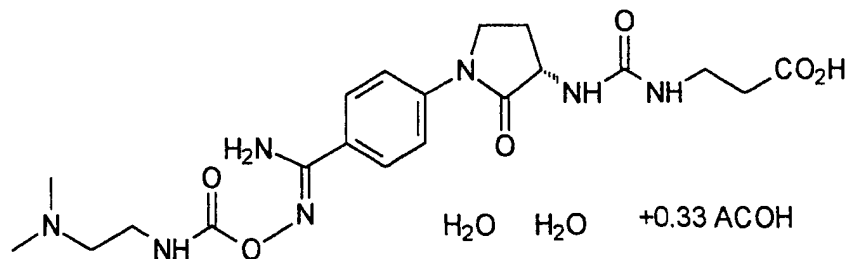
C, 41.50; H, 4.88; N, 13.55.

Found: C, 41.46; H, 4.58; N, 13.68.

15

#### Example 6 (b)

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine



20

The product was repurified by RPHPLC using HOAc in the mobile phase.

5 m. p. 149-154°C (dec.).

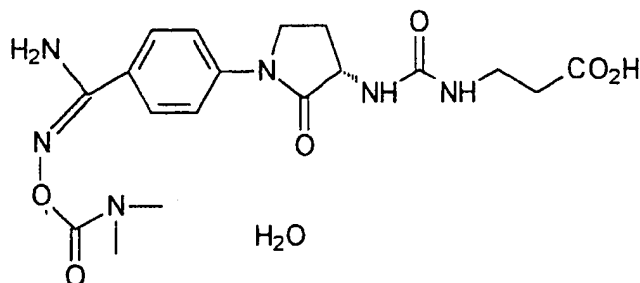
Analysis calculated for  $C_{20}H_{29}N_7O_6 \cdot 0.33 \text{ HOAc} \cdot 2.0 \text{ H}_2\text{O}$ :

C, 47.78; H, 6.66; N, 18.87.

Found: C, 47.83; H, 6.55; N, 18.82.

10 Example 6 (c)

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine monohydrate



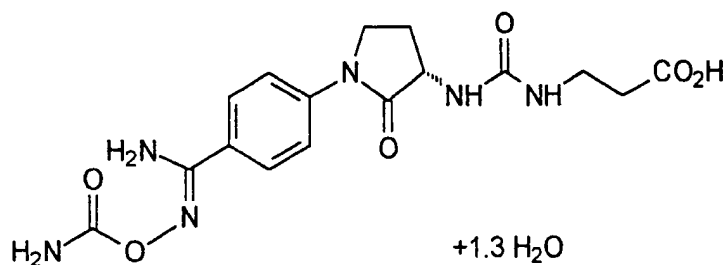
15 m. p. 175-178°C.

Analysis calculated for  $C_{18}H_{24}N_6O_6 \cdot 1.0 \text{ H}_2\text{O}$ : C, 49.31; H, 4.98; N, 19.17.

Found: C, 49.22; H, 6.10; N, 19.15.

Example 6 (d)

20 N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine



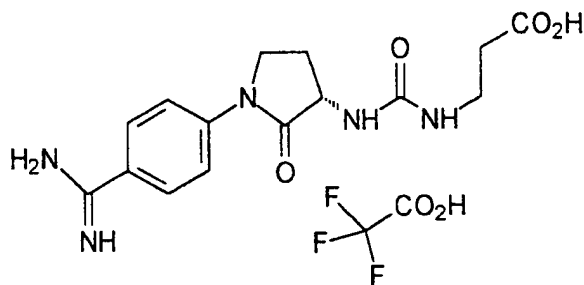
5 m. p. 135-140°C (dec.).

Analysis calculated for  $C_{16}H_{20}N_6O_6 \cdot 1.3 H_2O$ : C, 46.22; H, 5.48; N, 20.21.

Found: C, 46.27; H, 5.30; N, 20.08.

Example 6 (e)

10 N-[[[(3S)-1-[4-(Aminoiminomethyl)phenyl]-2-oxo-3-pyrrolidinyl]amino]-  
carbonyl]-β-alanine trifluoroacetate. Reference compound 1 (RF1)



m.p. 222-223°C (dec.).

15 Analysis calculated for  $C_{15}H_{19}N_5O_4 \cdot 1.0 TFA \cdot 1.0 H_2O$ :

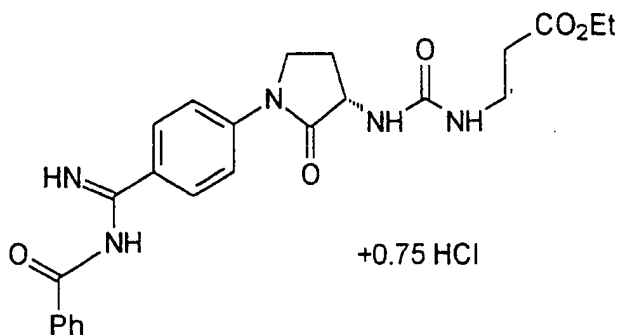
C, 45.64; H, 4.51; N, 15.66.

Found: C, 45.51; H, 4.36; N, 15.78.

5

Example 7

N-[[[3(S)-1-[4-[imino[(phenylcarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine ethyl ester



10

To a room temperature, stirred solution of the product of Example 2(a) (2.50 g, 5.97 mmol) and sodium bicarbonate (2.00 g, 23.7 mmol) in acetonitrile/water (20 mL) (1:1) was added benzoyl chloride (2.50 g, 17.8 mmol). After 2 hours of vigorous stirring, the reaction mixture was diluted with water and diethyl ether. The resulting biphasic suspension was filtered, washed with water then ether and dried. Recrystallization from EtOH afforded the product (800 mg) as the free base. The compound was converted to the HCl salt by suspending the solid in water (10 mL) and adding 2N HCl (1 mL). The resulting solution was lyophilized to give the product (860 mg) (m. p. 210-211°C).

20

Analysis calculated for  $C_{24}H_{27}N_5O_5 \cdot 1.75 \text{ HCl}$ : C, 54.46; H, 5.47; N, 13.23.

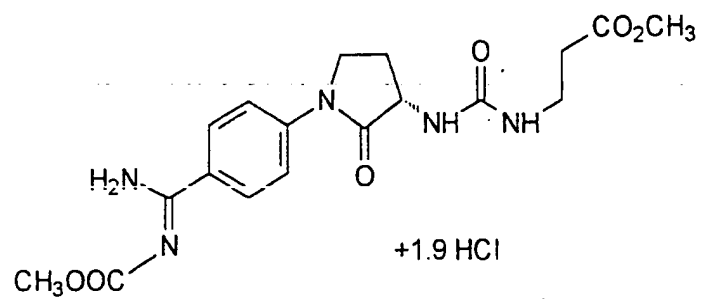
Found: C, 54.48; H, 5.25; N, 13.23.

The following compound was prepared analogously:

25

Example 7 (a)

N-[[[3(S)-1-[4-[imino[(methoxycarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-β-alanine methyl ester



m. p. 165-166°C (dec.).

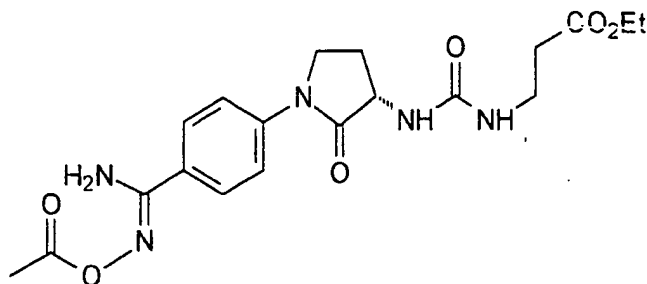
Analysis calculated for  $C_{18}H_{23}N_5O_6 \cdot 1.9 \text{ HCl}$ : C, 45.55; H, 5.29; N, 14.75.

Found: C, 45.59; H, 5.09; N, 14.89.

5

Example 8

Preparation of N-[[[(3S)-1-[4-[[[(acetyloxy)amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester



10 To a room temperature, stirred solution of the product of Example 1 (1.00 g, 2.65 mmol) in pyridine (6 mL) was added slowly acetic anhydride (0.27 g, 2.65 mmol). After 30 minutes of stirring the thick reaction mixture was diluted with water (25 mL) and the pyridine neutralized to pH 6-7 with concentrated HCl (~6 mL). After stirring an additional hour, the white  
15 precipitate was filtered, washed with water and dried affording the product (810 mg, 73% yield) [m. p. 188-189°C (dec.)].

Analysis calculated for  $C_{19}H_{25}N_5O_6$ : C, 54.41; H, 6.01; N, 16.70.

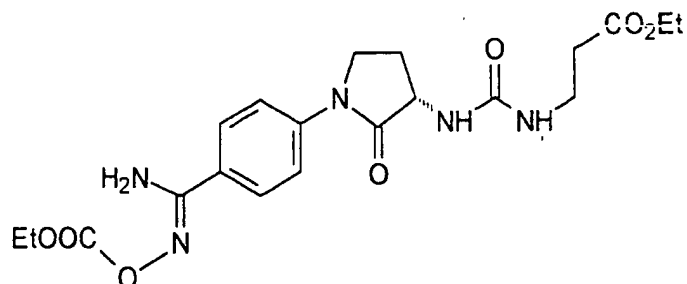
Found: C, 54.16; H, 5.77; N, 16.75.



5

### Example 9

Preparation of N-[[[(3S)-1-[4-[[[(ethoxycarbonyl)oxy]amino]imino-  
methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester



10 To a room temperature, stirred solution of the product of Example 1  
(1.05 g, 2.78 mmol) in pyridine (6 mL) was added slowly ethyl chloroformate  
(0.30 g, 2.78 mmol). After 15 minutes of stirring the clear solution was diluted  
with water (40 mL) and the pH adjusted to 3 with concentrated HCl (~5.5 mL).  
The white precipitate was filtered, washed with water and dried affording the  
15 product (1.00 g, 80% yield) (m. p. 198-201°C).

Analysis calculated for  $C_{20}H_{27}N_5O_7$ : C, 53.45; H, 6.06; N, 15.57.

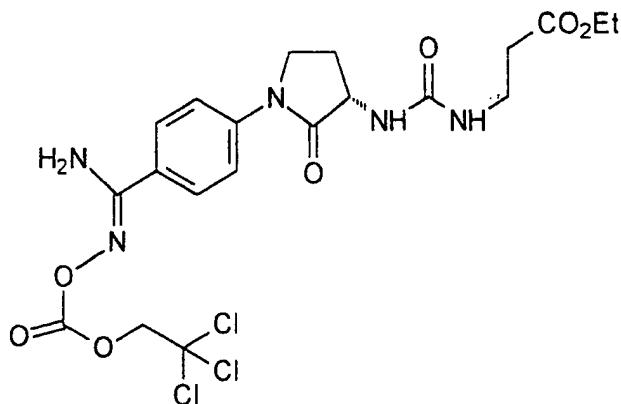
Found: C, 53.36; H, 6.37; N, 15.55.

5

Example 10

Preparation of N-[[[(3S)-1-[4-[imino[[[(2,2,2-trichloroethoxy)carbonyl]oxy]-amino]methyl]phenyl]-2-oxo-3-pyrrolidiny]amino]carbonyl]-

$\beta$ -alanine ethyl ester



10

The title compound was prepared from the product of Example 1 (1.05 g, 2.78 mmol) and 2,2,2-trichloroethyl chloroformate (0.59 g, 2.78 mmol) in a manner similar to Example 6 affording the product (1.13 g, 74% yield) after trituration and filtration from ether. (m. p. 196-198°C).

15      Analysis calculated for  $C_{20}H_{24}N_5O_7Cl_3$ :              C, 43.46; H, 4.38; N, 12.67.  
   Found:              C, 43.17; H, 4.27; N, 12.67.

5

Example 11*Ex Vivo Screening of Oral GP IIb/IIIa Inhibitors*

Beagles (8-13 kg, various sources) of either sex are dosed orally with compound in a gelatin capsule. Blood samples are drawn from the cephalic vein using a 23 ga infusion butterfly. Samples for platelet aggregation and drug concentration are taken prior to dosing and 0.5, 1, 2, 3, 5, 7 and 10 hours after dosing and periodically on subsequent days until inhibition of platelet aggregation is less than 30%. Animals are fasted, with ad lib access to water, overnight prior to dosing. For measurement of plasma concentration blood is drawn into a 3 ml tube containing 45 USP units of Na Heparin. Blood is centrifuged at 1700 xg for 10 minutes, plasma is aspirated and frozen at -20° C until analyzed by HPLC. For measurement of platelet aggregation, blood is drawn into 2 2.0 ml tubes containing 0.2 ml of 3.8% Na Citrate. Blood is centrifuged at 250 xg for 6 minutes and the platelet rich plasma (PRP) is aspirated. The remaining blood is centrifuged at 1700 xg for 10 minutes and platelet poor plasma (PPP) is aspirated. Platelet aggregation is performed in a Bio-Data PAP-4 aggregometer (Bio-Data Corp., Havertown, PA) using collagen (100 µg/ml final concentration; Helena Laboratories, Beaumont, TX) as the agonist. Briefly, baseline (100% aggregation) is set using PPP; PRP is incubated at 37°C for one minute without stirring and one minute with stirring, agonist is added and aggregation is allowed to develop for 4 minutes. Percent aggregation post-dosing is compared to percent aggregation pre-dosing to determine percent inhibition. The calculated percent inhibition at 32 hours post-dosing is reported in the following Table 1.

30

5 Table 1: Percent inhibition of platelet aggregation at 32 hour post-dosing in  
beagle dogs (5-mpk, n = 2).

	<u>Example #</u>	<u>% inhibition @ 32 hours</u>
	1	95
10	1(a)	85
	1(b)	71
	1(c)	94
	1(d)	45
	1(f)	87
15	1(h)	39
	3	66
	3(a)	33% @ 26 hours
	3(b)	54
	3(d)	88% @ 26 hours
20	3(e)	54
	3(f)	35
	3(g)	69
	3(h)	56
	3(j)	34
25	3(l)	71
	3(m)	80
	3(n)	73
	3(q)	57
	3(r)	46
30	3(u)	63
	3(cc)	22
	3(ff)	70
	4	68
	4(a)	63

	<u>Example #</u>	<u>% inhibition @ 32 hours</u>
5	4(b)	20
	4(c)	64
	5	89
	5(a)	82
10	5(b)	64
	5(h)	28
	6(a)	61% @ 10 hours
	6(d)	15% @ 10 hours
	6(e) (RF1)	28% @ 10 hours
15	7	53
	8	57
	9	90
	10	84

5

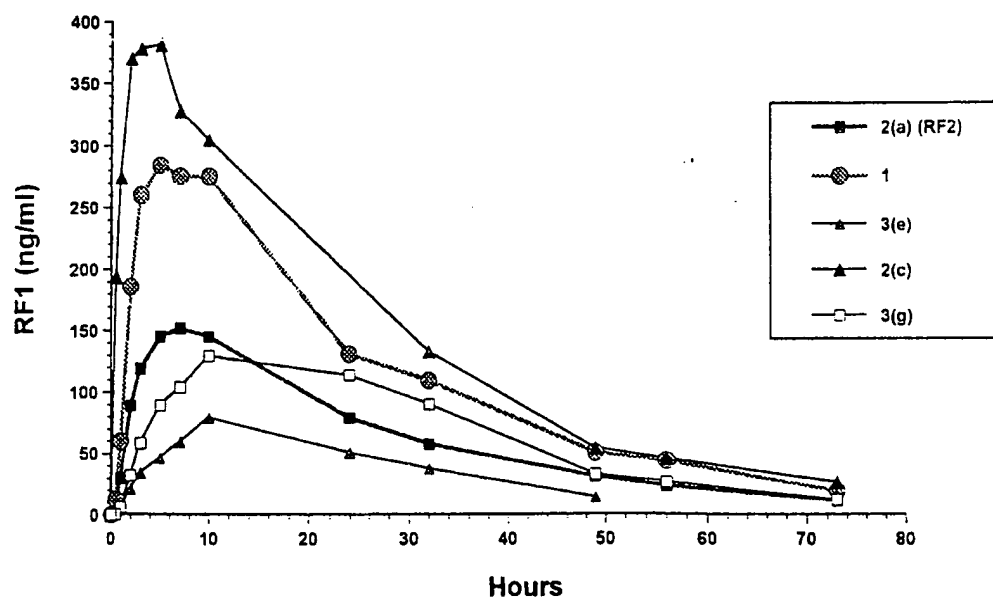
Example 12Plasma Concentration Analysis

An HPLC method was employed to determine RF1 concentrations in dog plasma using an appropriate internal standard. The procedure consists of a solid phase extraction of RF1 from dog plasma using a C18 extraction column (100 mg Isolute C18 MF). To 0.25 mL of dog plasma, 0.50 mL of 0.05 N HCl and 100 µL of internal standard solution were added and mixed thoroughly using a vortex mixer. The solid phase extraction process was performed using a Zymark RapidTrace automated extraction system. The C18 column was activated using 1 mL of methanol followed by 1 mL of water. The sample was then loaded into the C18 extraction column and extracted using positive pressure. The C18 extraction column was then washed with 2 mL of water followed by 0.5 mL of acetonitrile. The compounds of interest were then eluted from the C18 extraction column using three 0.5 mL aliquots of 0.2% tetra-ethylammonium phosphate (TEAP) (pH 2.5) and methanol (5:95, by volume). The extract was taken to dryness with nitrogen and reconstituted with HPLC mobile phase A, 10% methanol/90% 80mM ammonium acetate (pH 4.0). The sample was injected onto a reverse phase HPLC.

HPLC analysis was performed on system equipped with a Hewlett-Packard 1050 pump, a Waters 717 autosampler and a Waters Symmetry C18 HPLC column (4.6x100mm) at 30 degree C with a Sentry Guard Column Nova-Pak C18 (3.9x20mm). The analytical run consisted of mobile phase A (10% methanol/90% 80mM ammonium acetate (pH 4.0)) isocratically for 5 minutes, a linear gradient to mobile phase B (50% or 60% methanol/50% or 40% 80mM ammonium acetate, pH 4.0) over 10 minutes, a return to mobile A over 5 minutes and a re-equilibration with mobile phase A for 10 more minutes before the next injection. The flow rate was 1.0 mL/minutes. The analyte was quantitated by the peak height ratios to the internal standard using a fluorescent detector at an excitation wavelength of 280nm and an

- 5 emission wavelength of 370nm. The plasma concentrations of RF1 in dog plasma after administration of selected compounds are graphically illustrated in Table 2.

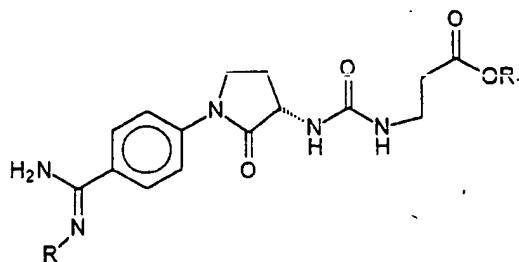
Table 2  
Plasma Levels of RF1 After a 5 mpk Oral  
Dose of Prodrugs in Dogs



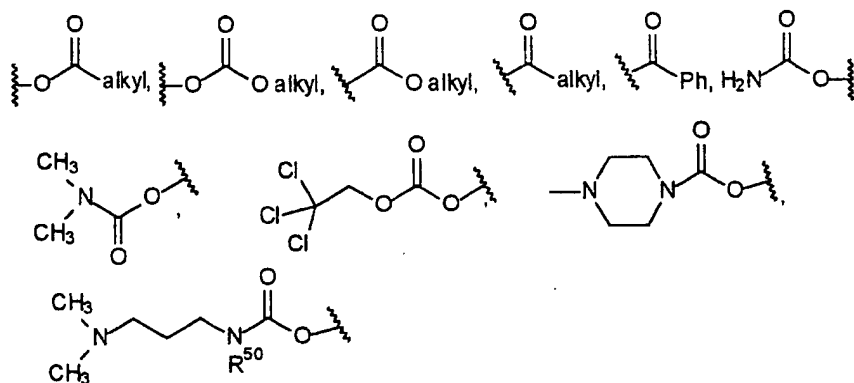


What is claimed is:

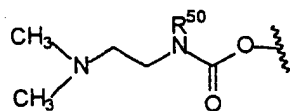
1. A compound of the formula



wherein  $R_1$  is selected from the group consisting of lower alkyl of about 2 to about 8 carbon atoms, cycloalkyl, and aralkyl;  $R$  is selected from the group consisting of alkoxy,



wherein  $R^{50}$  is H or alkyl; and



wherein  $R^{50}$  is H or alkyl; and pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 selected from the group consisting of

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine methyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]-methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2-methylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-5,9-dimethyl-4-oxo-3-oxa-2,5,9-triazadec-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny)carbonyl]oxy]amino]-methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine  
2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperaziny)carbonyl]oxy]amino]methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]imino-methyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]-phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine cyclohexyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine pentyl ester;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1,1-dimethylethyl ester;

N-[[[(3S)-1-[4-[imino[[[(4-methyl-1-piperazinyl)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-(1-imino-5,8-dimethyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-(1-imino-8-methyl-4-oxo-3-oxa-2,5,8-triazanon-1-yl)]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-[[[(dimethylamino)carbonyl]oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-[[[(aminocarbonyl)oxy]amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine;

N-[[[(3S)-1-[4-[imino[(phenylcarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;



N-[[[(3S)-1-[4-[imino[(methoxycarbonyl)amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[(acetyloxy)amino]iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[(ethoxycarbonyl)oxy]amino]imino-methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester; and

N-[[[(3S)-1-[4-[imino[[[(2,2,2-trichloroethoxy)carbonyl]oxy]amino]methyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.
4. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 2 and a pharmaceutically acceptable carrier.
5. A pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of:

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine propyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine butyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2,2-dimethylpropyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine pentyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1,1-dimethylethyl ester;

or a pharmaceutically acceptable salt thereof and a pharmaceutically therapeutic carrier.

6. A method of inhibiting platelet aggregation in a mammal in need of such treatment comprising administering a therapeutically effective amount of a compound of a formula according to Claim 1.
7. A method of inhibiting platelet aggregation in a mammal in need of such treatment comprising administering a therapeutically effective amount of a compound of a formula according to Claim 2.
8. A method of inhibiting platelet aggregation in a mammal in need of such treatment comprising administering a therapeutically effective amount of a compound selected from the group consisting of:

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine ethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine methyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 1-methylethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine propyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine 2-methylpropyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]-β-alanine butyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 2,2-dimethylpropyl ester;

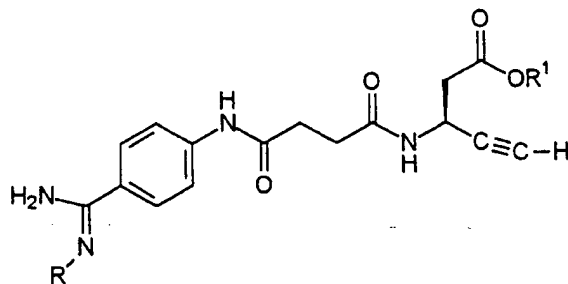
N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine phenylmethyl ester;

N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine pentyl ester;

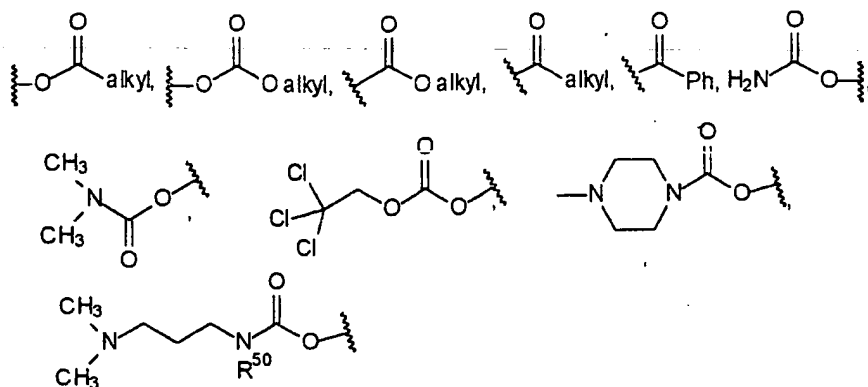
N-[[[(3S)-1-[4-[(hydroxyamino)iminomethyl]phenyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]- $\beta$ -alanine 1,1-dimethylethyl ester;

or a pharmaceutically acceptable salt thereof.

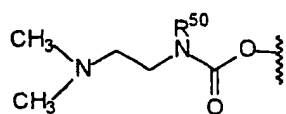
9. A compound of the formula



wherein  $R_1$  is selected from the group consisting of H, lower alkyl of about 2 to about 8 carbon atoms, cycloalkyl and aralkyl; R is selected from the group consisting of OH, alkoxy,



wherein  $R^{50}$  is H or alkyl; and



wherein  $R^{50}$  is H or alkyl; and pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 9 and a pharmaceutically acceptable carrier.
11. A method of inhibiting platelet aggregation in a mammal in need of such treatment comprising administering a therapeutically effective amount of a compound of a formula according to Claim 9.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11799

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D207/26 A61K31/40 C07C259/18

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 22820 A (SEARLE & CO ;ABOOD NORMAN ANTHONY (US); FLYNN DANIEL LEE (US); GAR) 13 October 1994 (1994-10-13) cited in the application abstract; claims page 46 -page 47; example 7 page 55 -page 57; examples 13,14	1,3,6, 9-11
Y	WO 96 17827 A (SEARLE & CO ;ABOOD NORMAN ANTHONY (US); FLYNN DANIEL LEE (US); LAN) 13 June 1996 (1996-06-13) cited in the application abstract; claims page 32 -page 43; examples 6,7,10,11,15,16	1,3,6, 9-11
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 November 1999

Date of mailing of the international search report

30/11/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11799

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 656 348 A (HOFFMANN LA ROCHE) 7 June 1995 (1995-06-07) cited in the application abstract; claims 1,19	1,3,6, 9-11
P,A	WO 98 34935 A (COOK JACQUELYNN J ;EGBERTSON MELISSA S (US); YOUNG STEVE D (US); M) 13 August 1998 (1998-08-13) abstract; claims	1,3,6, 9-11

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 11799

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6-8, 11  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 6-8, and 11  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/11799

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